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Editorial

Circulatory Regulation and Shifting in Hypoxia

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One of the basic conditions of animal life is adequate blood, i.e., oxygen supply. The uptake and transport of oxygen is altered in some conditions; consequently, different forms of hypoxia may develop, damaging the organism. The role of the "depot" organs, such as the spleen, is well known in the correction of blood distribution, as is the increase in circulation in certain organs during augmented activity, i.e., muscle, digestive organs, and in thermoregulation. The importance of each organ from the point of view of hypoxic damage depends on its importance to the whole organism. Such damage to the heart and brain may lead immediately to death; however, the organism may tolerate this disturbed function in other organs, such as the kidney, for a longer time. Accordingly, all mechanisms which deplete the blood of actually less important organs in preference to the brain and the heart, "shifting," may be in favor of life.[1-5]

The regulation of the circulation may be different in various types of hypoxia. Thus, the increase in cardiac output per se may result in an adequate blood supply for vital organs such as the heart and brain, but only to a certain extent. In other conditions the nature of the trouble itself excludes the possibility of an increase in the cardiac output. Therefore, we consider it reasonable to discuss two main groups of hypoxic states: (1) conditions in which the increase in cardiac output may result in so-called "hypervolemic" hypoxia; and (2) the decrease in flow or diminution of the circulating blood volume which leads to hypoxia itself, hence called "hypovolemic" hypoxia.

1. *Hypervolemic Hypoxia.*—In this group we may consider *arterial hypoxia* (anoxic anoxia) of high altitudes, and certain diseases of the chest, such as chronic emphysema complicated with acute pneumonia or bronchitis. These may be produced experimentally with ease by the inhalation of air under reduced pressure,

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or a gas mixture poor in oxygen. *Anemic hypoxia* occurs in certain anemias, i.e., the inability of hemoglobin to transport oxygen. In *extreme muscle activity* hypoxia may develop because of increased oxygen demand. Arterial hypoxia has been extensively investigated and may be used as an example of hypervolemic hypoxia. In arterial hypoxia the cardiac output increases, whereas the total peripheral resistance of the circulation diminishes.[1-3] But the vessels of the *kidney* do not take part in this general vasodilation; the blood flow of the kidney, hence the renal fraction of the cardiac output, decreases, and thus the circulatory resistance of the kidney will increase.[1-3,6] The role of the nervous system in the constriction of the vessels of the kidney has recently been investigated in dogs: under chloralose anesthesia, isolated head circulation was produced by a Dale-Schuster pump. By reducing the oxygen saturation of the blood flowing through the isolated head, the blood flow of the kidney (C_{PAH}), i.e., the renal fraction of the cardiac output, decreases, and the circulatory resistance increases, just as occurs in hypoxia systemically, without any alterations of the cardiac output or blood pressure. These changes are reversible. The C_{PAH} also decreases in isolated hypercapnia, in isolated hypotension, and with reduced flow in the isolated head produced by narrowing of the tubes leading to it. Under these conditions, as a result of the vasoconstriction in the kidney, even anuria developed in some cases. Denervation of the kidney or dibenamine prevents the decrease in renal blood flow; adrenalectomy or the denervation of both carotid sinuses does not have any effect. These experiments may indicate that receptors are located in the head (brain), which can be stimulated by hypoxia, hypercapnia, and hypotension with stagnant hypoxia; the nervous stimuli are conducted by sympathetic fibers to the kidney.[1-3] It has been shown quite recently that the branches of the *hepatic artery* may also be constricted in severe hypoxia.[7]

During vasoconstriction of the kidney the *coronary* blood flow increases considerably, the circulatory resistance of the coronaries decreases, but, according to new investigations, the coronary fraction of the cardiac output increases.[1,8] All these data prove that shifting to the coronaries really does exist. In the improvement of the coronary circulation the active dilatation of the coronary branches has a role, too. There is difficulty in evaluating shifting toward the *brain* because in animal experiments the extracranial circulation may modify the results of direct measurement. Fortunately, some results obtained by nitrous-oxide and other methods prove the increase in the blood flow of the brain and the decrease of resistance in hypoxia.[9-11]

There is no evidence available concerning the *mechanism* of the increase in cardiac output in hypoxia. Attempts to demonstrate a higher regulatory mechanism have failed until now. The isolated hypoxia of the head does not influence the cardiac output. This hypoxic increase in cerebral flow cannot be prevented by sympathetic section or adrenalectomy; the available data are still contradictory. Most probably the old theory of arteriolar dilatation, i.e., the consequent increase of venous return leads to increased filling of the heart and to an increase in its output, still holds.[1-3,12,13]

2. *Hypovolemic Hypoxia.*—We may consider in this group the different types of shock, hemorrhage, dehydration, and, to a certain extent also, heart

failure. The increase of arteriovenous oxygen difference, i.e., stagnant hypoxia, as a result of the slowing of the circulation is common to all of them. The decrease in cardiac output is well known in shock, hemorrhage, and dehydration, and we may find similar alterations in severe cardiac failure.

The considerable increase of *total peripheral resistance* in traumatic shock[8,14,15] and after burns[16] is well established; it occurs generally in dehydration also,[17-19] and it may develop in hemorrhage but not in every case. In tourniquet shock[20,21] the enormous vasodilatation of the damaged extremity conceals the increase in total peripheral resistance. The total peripheral resistance increases in cardiac failure also.[22] There are several experiments concerning the *kidney* which establish the decrease in renal blood flow, a decrease in the the renal fraction of cardiac output, and the increase in circulatory resistance of the kidney in these conditions.[4,5,19,22-25] The circulation of the intact *extremity* and the extremity fraction of cardiac output diminishes and the resistance increases in hemorrhage, dehydration, and shock.[14,20,26,27] There is evidence of vasoconstriction in the *splanchnic area* also.[21,28,29]

According to available data, we may find, in spite of oligemia, only a slight decrease in *coronary* blood flow in hemorrhage and traumatic shock; hence, the circulatory resistance of the coronaries is low, and the coronary fraction of cardiac output is evidently increased.[30-33] In dehydration the coronary fraction of cardiac output decreases but the resistance remains unaltered[8]: so the coronaries, in fact, do not take part in the general vasoconstriction. Thus, a sufficient coronary circulation is secured only by shifting without dilatation of the coronary branches. The circulation of the *brain* has been investigated, too. The head fraction of cardiac output increases in dogs in ischemic shock,[34] and the circulatory resistance of the head remains constant in spite of the increase in total peripheral resistance. It has been proved by fenestration of the skull in dogs that the diameter of the vessels of the pia does not change in shock.[35] As supposed, the cerebral blood flow is independent of the systemic blood pressure, which indicates the possibility of active vasodilatation.

The role of the kidney in shifting was recently criticized in hemorrhage and dehydration.[17,36] Discrepancies were found between the direct and indirect (C_{PAH}) determinations of the renal blood flow.[17,36] There is doubt that the results of C_{PAH} are reliable in intense oliguria. An ingenious new method[37] using *isotope extraction* of the organs furnishes real progress in solving this problem. The earlier results were corroborated by this method (K^{42}), which proved the shifting from the kidney toward the heart in *hemorrhage*. According to these experiments the renal fraction of the cardiac output decreased from 19.4 to 10.1 per cent, whereas the coronary fraction increased from 2.2 to 8.5 per cent.[38] The same was found recently with Rb^{86}.[39]

In *dehydration* the arterial ischemia of the kidney has been demonstrated with the *corrosion method* too. Kidneys were injected from the renal artery with polyvinyl chloride dissolved in cyclohexane. After corrosion, considerable defects were seen in the arterial and/or glomerular filling (arterial ischemia). The venous system showed evidence of retrograde filling through arteriovenous anastomoses. It is quite possible that the diversion of the blood from the kidney is

caused by arterial vasoconstriction and/or by opening of arteriovenous shunts. This was found to a lesser degree in shock, hemorrhage, and arterial hypoxia.[40]

In conclusion, it seems very likely that there is shifting in some hypoxic conditions to the brain and coronaries. The role of the kidney has been most thoroughly studied. This organ seems to be very suitable for this purpose, because of its high blood supply, 20 per cent, and small arteriovenous oxygen difference, 1 to 3 per cent. Long-lasting ischemia, however, may lead to severe renal failure, as is well known. Shifting is especially useful for the coronaries, because of their very high arteriovenous oxygen difference, 10 to 13 per cent, which makes a further increase of oxygen extraction quite impossible; hence, only an augmentation of coronary blood circulation can improve the oxygen supply of the heart. The shifting to the coronaries and brain apparently protects the patients in severe shock from immediate death.

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Clinical Communications

Alteration of Serum Enzymes in Clinical Myocardial Infarction

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Reports that certain enzyme determinations are valuable adjuncts in the diagnosis of myocardial infarction have stimulated this laboratory to study the relationship of the activities of serum glutamic oxalacetic transaminase (SGO-T), serum lactic dehydrogenase (LD), and serum malic dehydrogenase (MD) following myocardial infarction. All of these enzymes have been reported by various investigators on different occasions to be significantly elevated in myocardial infarction, but no comparison has been made of all three on the same sample of serum.[1-6]

This study, which has been going on for the past 3 years, encompasses the determination of serum glutamic oxalacetic transaminase, serum lactic dehydrogenase, and serum malic dehydrogenase on a single sample obtained in patients hospitalized with a variety of clinical conditions.

Over 200 patients hospitalized for a wide variety of clinical conditions were studied. Patients included those with pulmonary tuberculosis, diabetes mellitus, liver disease, sickle cell anemia, cerebrovascular accidents, congestive failure, pulmonary infection, neurological disease, and other miscellaneous conditions.

The study was primarily directed, however, toward the value of these enzymes in the support of the diagnosis of myocardial infarction. For this purpose, serial determinations on the same sample of serum were obtained on a large number of patients who had sustained an unquestionable myocardial infarction. In all cases, the diagnosis was based on history, serial electrocardiographic changes, elevation of WBC and sedimentation rate, and positive CRP. The presumed time of occurrence of the infarct was based upon the history of onset of chest pain, syncope, nausea, vomiting, dyspnea, or collapse.

METHODS EMPLOYED IN MEASUREMENT OF ENZYMES

The enzyme activities were determined spectrophotometrically, some determinations being made with the B & L Spectronic 20, and the remainder in the Beckman DU spectrophotometer.

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With both instruments, the enzymatic activity was estimated in terms of the rate of change of optical density of the buffered reaction mixture (1/15M phosphate buffer, pH 7.4) in the presence of a known volume of serum, 1 mg. of reduced diphosphopyridine nucleotide (DPNH), and an excess of the appropriate substrate, aspartate + a-ketoglutarate, oxalacetic, or pyruvate. For all of the determinations the unit of enzyme activity was taken as a change of 0.001 optical density per minute. Other details of the assays for the individual enzymes follow.

Serum Glutamic Oxalacetic Transaminase[1].—By using 0.1 mM. of aspartate + .02 mM. a-ketoglutarate as substrate and supplementing the basic mixture with a commercial preparation of malic dehydrogenase, it was possible to assay the rate of conversion (transamination) of aspartate to oxalacetate, since, in the presence of excess malic dehydrogenase, the oxalacetate was converted to malate as fast as the oxalacetate was formed. The reduction of oxalacetate to malate requires an equimolar oxidation of DPNH to DPN, and it is this oxidation which causes the fall in optical density in the near ultraviolet (peak absorption of DPNH is at 340 mμ).

$$\text{(1)}\quad \text{Aspartate} + \text{a-ketoglutarate} \xrightleftharpoons{\text{transaminase}} \text{oxalacetate} + \text{glutamate}$$

$$\text{(2)}\quad \text{Oxalacetate} + \text{DPNH} \xrightleftharpoons[\text{dehydrogenase}]{\text{malic}} \text{malate} + \text{DPN}$$

Therefore, the transamination was expressed in terms of change in optical density (O.D.) per minute effected by 1 ml. of serum. With the Beckman DU the wave length was 340 mμ, and the light path was 10 mm.; with the Spectronic 20, the wave length was 350 mμ, and the light path was 18 mm. Because of the optical difference between the two instruments, normal ranges were established for each.

Serum Lactic Dehydrogenase[7].—To the basic incubation mixture was added 2 mM. of pyruvate as substrate. With this combination the rate of conversion (reduction) of pyruvate to lactate was estimated, since, as shown in Reaction 3,

$$\text{(3)}\quad \text{Pyruvate} + \text{DPNH} \xrightleftharpoons{\text{lactic dehydrogenase}} \text{lactate} + \text{DPN}.$$

Pyruvate reduction is coupled with equimolar DPNH oxidation, so that the rate of pyruvate reduction is directly indicated by the rate of DPNH oxidation, which, in turn, can be measured by the rate of decrease of optical density at 340 mμ.

Serum Malic Dehydrogenase[8].—By adding 2 mM. of oxalacetate as substrate to the basic incubation mixture (buffer + DPNH) it was possible to measure the rate of conversion (reduction) of oxalacetate to malate, since, as shown in Reaction 2, oxalacetate reduction is coupled with DPNH oxidation. As stated above, the reduction of oxalacetate requires an equimolar oxidation of DPNH to DPN, and the oxidation of DPNH to DPN results in a fall of the optical density at 340 mμ of the reaction mixture. Enzyme activity was expressed as change in density at 340 mμ for the Beckman DU (350 mμ for the Spectronic 20) per minute per 1 ml. of serum.

In the initial phase of the study of all three enzymes, the B & L Spectronic 20 was used because we were fortunate enough to have a phototube in the instrument capable of giving full-scale deflection at 350 mμ. This seemed justified because the extinction of reduced DPNH at 350 mμ is within a few per cent of that at the 340 mμ maximum. An advantage of this instrument is that twelve samples can be examined in a 10-minute period by a trained operator, whereas the Beckman DU requires that samples be treated in groups of three.

Using the Spectronic 20, 10 normal subjects, 5 men and 5 women, ranging in age from 19 to 64 years, served as normal controls for the determination on a single sample of all three enzymes, SGO-T, LD, and MD activities. The results are shown in Table I.

In the Spectronic-20 series, 30 patients who sustained an unequivocal myocardial infarction were studied for the serial determinations of all three enzymes on a single sample. There were 12 deaths, 11 of which were confirmed at autopsy as being due to myocardial infarction. Four were cases of convalescent infarcts over a week old, and 2 patients died within less than 24 hours. Fig. 1 is a scatterogram of 30 patients with myocardial infarction.

The next phase of the study using the Beckman DU was the result of the failure to procure another phototube sensitive to 350 mμ when the original tube sensitive to 350 mμ in the Spectronic

20 could no longer give full deflection at 350 mμ. In order to get a much better sampling of normal values on single samples of serum, 50 healthy adults, 42 males and 8 females, ranging in age from 22 to 58 years, served as controls. These subjects were ambulatory and were not hospital patients, and the enzyme activities were determined without regard to intake of food or physical exertion or time of day. Results with the Beckman DU are as shown in Table II. In this series, 12 patients with unequivocal myocardial infarction were studied (see Fig. 2).

Eleven other hospitalized patients who were suspected of having a myocardial infarct because of the appearance of, or complaint of, chest pain were also studied. This series included 1 case of hyperthyroidism, 1 case of Felty's syndrome, 6 cases of arteriosclerotic heart disease with angina, 2 cases of hypertensive cardiovascular disease, and 1 case of pulmonary emphysema. In none of these cases was there a significant elevation of the SGO-T, LD, or MD, except in one instance (T.J.) of hypertensive cardiovascular disease in which the LD was slightly elevated, and in the case of Felty's syndrome with pericarditis, in which the LD was also slightly elevated. Table III summarizes the 11 cases of suspected infarct.

TABLE I

Spectronic 20 10 normal pts.

	SGO-T	LD	MD
Range	0–35	180–244	82–202
Mean	19 ± 8.4	200 ± 24.5	129 ± 37.5

TABLE II

Beckman D U 50 normal pts

	SGO-T	LD	MD
Range	10–45	100–260	80–310
Mean	22.7 ± 7	174 ± 40	160 ± 54

RESULTS

In the Spectronic-20 series, the SGO-T, LD, and MD activities of 30 patients with proved myocardial infarction were elevated two to three times above the normal range (see Fig. 1). The solid line represents the daily mean of all determinations on experimental subjects, and the dotted line represents the normal mean. It will be noted that the SGO-T activity returns to normal within 5 days following the myocardial infarction, whereas the LD and MD activities remain elevated up to 10 days.

In the Beckman-DU series (Fig. 2) the SGO-T, LD, and MD activities of 12 patients with myocardial infarction were also elevated two to three times above normal, the lactic tending to be relatively higher than the malic. In this series the SGO-T returns to normal within 5 days, and the lactic and malic tend to remain elevated up to periods of 14 days following myocardial infarction.

Fig. 3 shows the relationship of the activities of SGO-T, LD, and MD in a typical patient following myocardial infarction. This was a 39-year-old white man who, while lecturing in an Army Reserve Unit, on Sept. 18, 1957, suddenly

developed precordial pain and cold sweat, and blacked out. He was immediately hospitalized, and an electrocardiogram revealed an acute posterior wall myocardial infarction. On September 19, the SGO-T was 170 units, the LD was 832 units, and the MD was 760 units, as determined with the Beckman DU spectrophotometer. The SGO-T returned to normal within 5 days, whereas the LD and MD were elevated up to the thirteenth day, returning to normal on the fourteenth day. The patient subsequently died of a viral bronchopneumonia, and an autopsy confirmed the diagnosis of transmural myocardial infarction.

Although the major effort was directed toward the study of myocardial infarction, the enzyme activities in other clinical entities were also investigated, and the data in these disease states were obtained similarly by the use of the Spectronic 20 and the Beckman DU.

TABLE III. SGO-T, LACTIC, AND MALIC DEHYDROGENASE ACTIVITY OF PATIENTS WITH DIAGNOSIS OF SUSPECTED MYOCARDIAL INFARCT

CASE	PATIENT	AGE (YR)	FINAL DIAGNOSIS	DAYS OF OBSERVATION	SGO-T	LD	MD
1.	E.C.	38	Hyperthyroidism with myocarditis. ECG: T-wave inversion in Leads I, II, III, AVL, AVF, V_5, V_6	1 2 3 4 5 6	26 38 6 19 29 20	228	230
2.	D.S.	61	ASHD with angina. ECG: Insufficiency	1	26	166	166
3.	L.S.	57	ASHD with angina. ECG: Left strain	1	38	282	158
4.	C.S.	63	Felty' syndrome with pericarditis. ECG: Inverted T wave in Leads I, II, III, AVL, AVF, and in V leads	1 2	10 49	270 385	15 68
5.	J.C.	59	ASHD with angina. ECG: Insufficiency	1	25	264	214
6.	S.C.	79	ASHD with angina. ECG: Nonspecific T-wave changes	1	19	195	16
7.	R.S.	58	Pulmonary emphysema, ASHD. ECG: Insufficiency	1	25	108	86
8.	C.D.	61	Pulmonary emphysema, ASHD with angina. ECG: Old posterior wall infarct	1	28	244	180
9.	F.H.	67	ASHD with angina. ECG: Old posterior wall infarct	1	43	214	158
10.	T.J.	64	HCVD. B.P., 226/124 mm. Hg. ECG: Left ventricular preponderance with abnormal S-T and T-wave changes	1 2 3 4	43 36 40 38	 332 322 404	 226 258 226
11.	F.B.	78	Hypertension. B.P., 240/140 mm. Hg. ECG: Left ventricular preponderance with S-T depressed and T wave inverted in Leads V_3, V_4, V_5, V_6	1	25	186	172

Pulmonary Disease.—Forty-two patients with pulmonary tuberculosis, all with positive sputum and with lesions varying from small infiltrates to advanced cavitary lesions, were studied. In none of the patients was there an elevation of SGO-T, LD, or MD, except in one patient with advanced pulmonary tuberculosis who developed a toxic hepatitis with jaundice as a result of therapy with

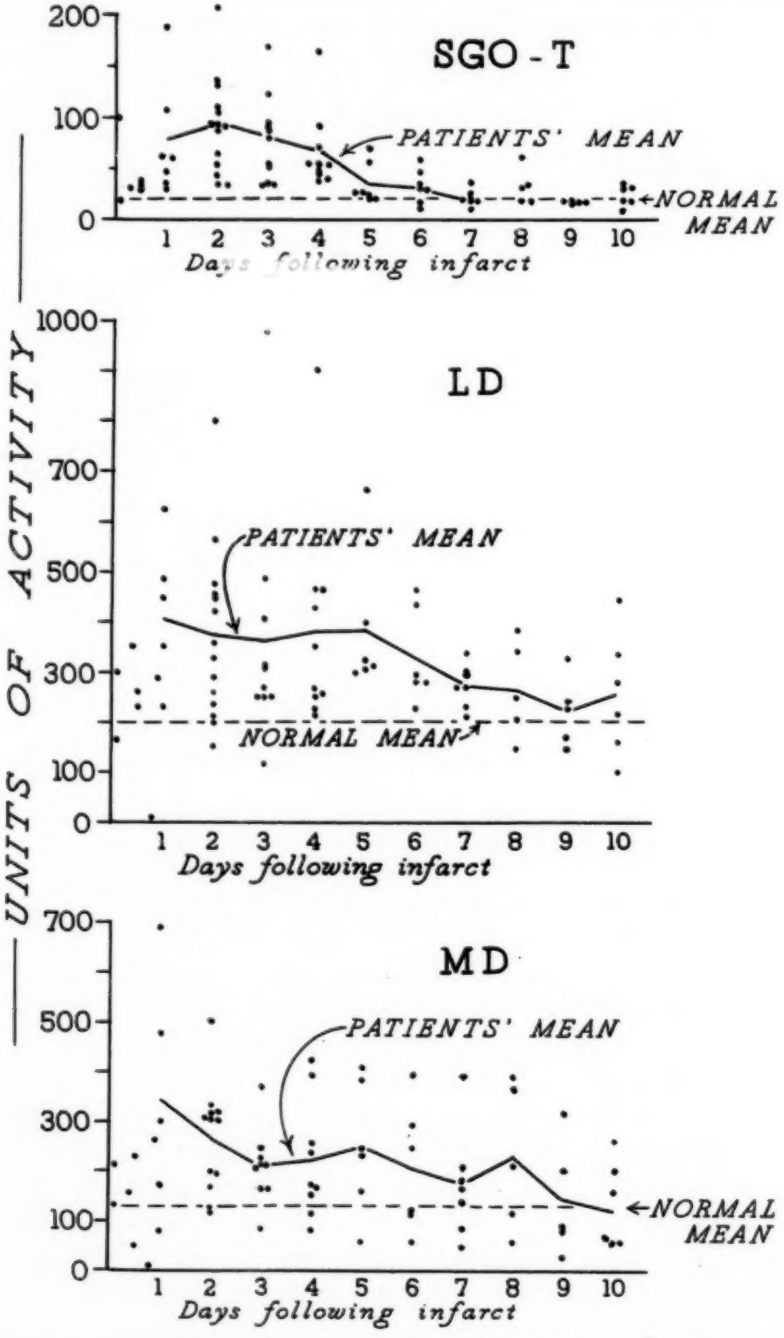

Fig. 1.—Spectronic-20 series. Serial determinations of SGO-T, LD, and MD activities in 30 patients with acute myocardial infarction.

para-amino-salicylic acid. He was a 34-year-old white man whose SGO-T level began to rise a few days before the onset of the drug sensitivity, reaching a level of 11,000 units within a week of the acute hepatitis. The LD and MD remained slightly elevated in the range of 350 to 400 units. All three enzyme determinations, however, returned to normal after the acute phase of the hepatitis had subsided. Four patients with lobar pneumonia had normal levels of all three enzymes, as did three patients with pulmonary emphysema.

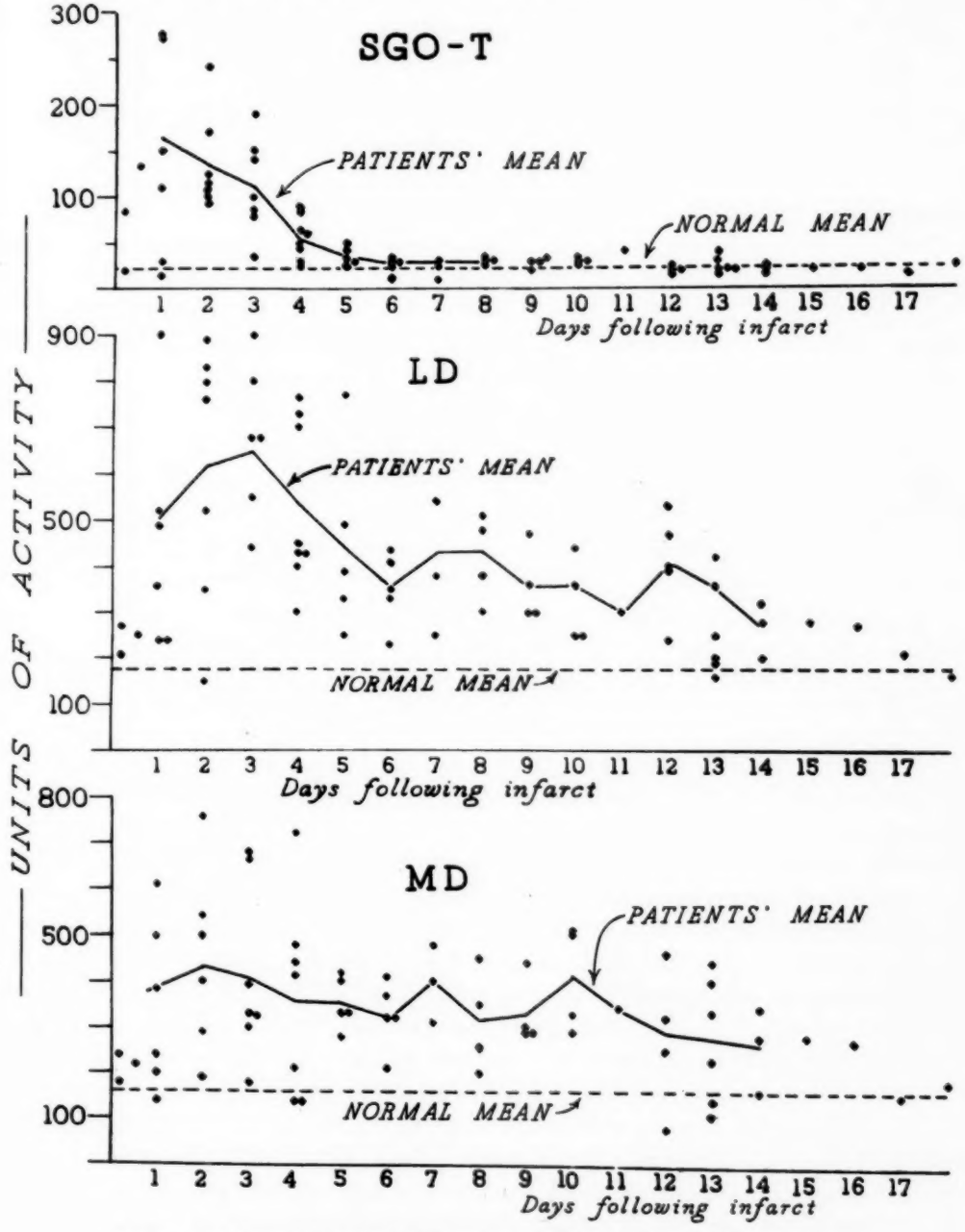

Fig. 2.—Beckman-DU series. Time course of SGO-T, LD, and MD activities in 12 patients with acute myocardial infarction.

Diabetes Mellitus.—Twenty patients with primary uncomplicated diabetes mellitus, 5 of whom were treated with DBI (Phenformin) instead of with insulin, had normal levels of SGO-T, LD, and MD activity. In 2 patients whose diabetes mellitus was complicated with cirrhosis of the liver, the SGO-T was elevated to a marked degree, whereas the LD and MD were also elevated but not proportionately.

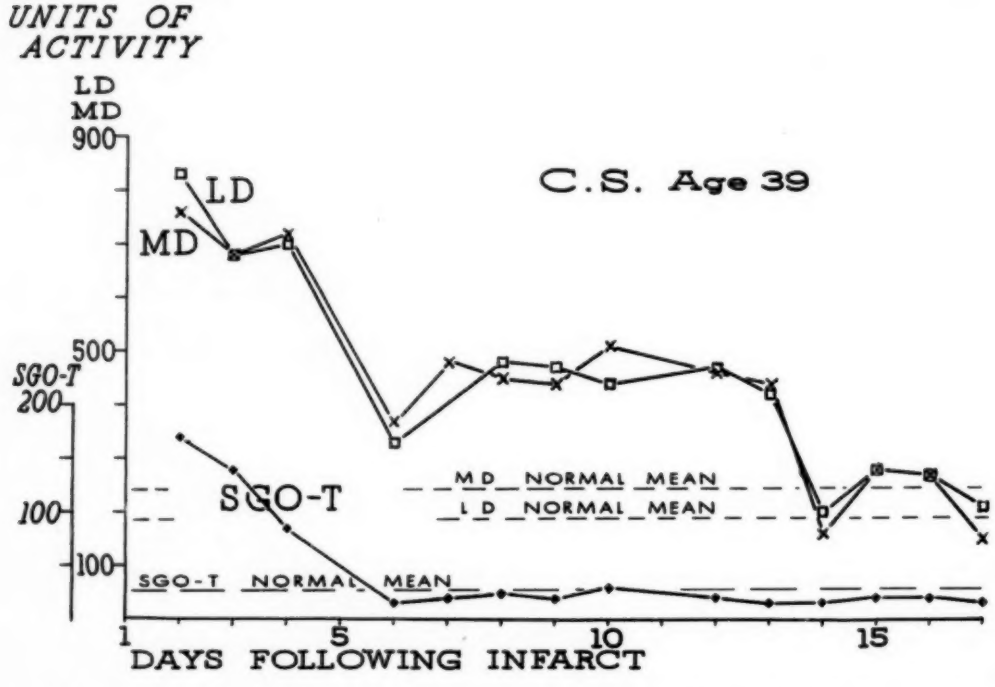

Fig. 3.—Relationship of SGO-T, LD, and MD activities in a typical patient with myocardial infarction. Note that the SGO-T has returned to normal 8 days before the LD and MD, which remain elevated in this instance up to 13 days following the presumed day of the onset of infarction.

Hepatitis.—Twenty patients with viral infectious hepatitis were studied during the active phase of the disease. All had elevated SGO-T levels four to six times the normal, and whereas the LD and MD levels were also elevated, they were only elevated one to two times over normal activity. In one instance, that of a 33-year-old white man, the SGO-T and LD were markedly elevated but the MD was not. It was our conclusion that of the three determinations, the SGO-T was the most valuable diagnostically and prognostically in viral hepatitis.

Infectious Mononucleosis.—There were 3 patients with infectious mononucleosis. In one of these the condition was complicated by hepatitis, and in this instance, all three enzymes were elevated during the acute phase of the hepatitis.

Cirrhosis of the Liver.—Forty patients with cirrhosis of the liver, in most of whom confirmation was made by liver biopsies, had serial determinations of SGO-T, LD, and MD. In all cases the SGO-T was significantly elevated, but the LD and MD were not of much aid in the diagnosis or the prognosis, since the values were either normal or slightly elevated and could not be correlated with the corresponding elevated SGO-T.

Sickle Cell Anemia.—Two patients with sickle cell anemia during crisis had constant elevation of all three enzymes, which returned to normal during the stage of remission. One patient had a mean (5 serial determinations) of 60 units of SGO-T, 950 units of LD, and 340 units of MD, and the other patient had a mean (10 serial determinations) of 100 units of SGO-T, 570 units of LD, and 470 units of MD.

Metastatic Liver Disease.—One patient with carcinoma of the pancreas with liver metastases and one patient with carcinoma of the lung with liver metastases showed elevation of all three enzymes.

Neurological Disease.—One patient with malignant thymoma and 3 with disseminated sclerosis had normal levels of SGO-T, LD, and MD, whereas 2 patients with progressive muscular dystrophy had elevation of all three enzymes.

Congestive Failure.—Congestive failure did not cause a rise in the levels of SGO-T, LD, and MD unless there was an accompanying congested liver. In only 3 out of 10 patients with congestive failure was there a large palpable liver, and in these the SGO-T, LD, and MD were elevated.

Malignant Hematological Diseases.—Two patients with lymphosarcoma, 2 with Hodgkin's disease, 3 with multiple myeloma, 2 with lymphatic leukemia, and 1 with myelogenous leukemia had elevations of all three enzymes to a moderate degree.

Pancreatitis.—Four patients with pancreatitis and 2 suffering from alcoholism had rises in the SGO-T but not in the LD or MD levels.

Cerebral Vascular Accidents.—Three patients with cerebral vascular accidents were studied. Only one of these had a rise in the levels of SGO-T, LD, and MD.

Miscellaneous.—The following patients had normal SGO-T, LD, and MD levels: one patient each with periarteritis nodosa, erythema multiforme, cholecystitis, erythema nodosa, and idiopathic pericarditis, and 2 patients each with rheumatic heart disease and pulmonary infarction.

DISCUSSION

Acute myocardial infarction resulting in necrosis of cardiac tissue presumably releases enzymes into the blood stream, resulting in the rise in enzyme activity of SGO-T, LD, and MD. These reach a peak within 24 to 48 hours, returning to normal within 5 days for SGO-T and within 10 to 14 days for LD and MD.

The rise in the activities of these enzymes is particularly helpful to the clinician in confirming the diagnosis of myocardial infarction when the electrocardiogram is not diagnostically significant of, or is obscured by, previous infarct, bundle branch block, Wolff-Parkinson-White syndrome, digitalis effect, or other electrocardiographic abnormalities, and particularly when the patient may be seen several days after the presumed onset of the infarct, at which time the lactic and malic levels are elevated.

Since the activity of MD closely parallels that of LD, it would seem that only one of these determinations should suffice in the average laboratory. The determination of LD is to be preferred over that of MD, because the determination of MD is technically more difficult to make.

SUMMARY

Forty-two patients with myocardial infarction were studied, and the results of alteration in the activities of SGO-T, LD, and MD are reported.

Whereas the enzyme activities of all three enzymes, SGO-T, LD, and MD, are usually elevated in infectious hepatitis, metastatic liver disease, and sickle cell anemia during crisis, they may also be elevated in cirrhosis of the liver and a variety of noncardiac conditions. However, the serially determined enzyme activities of all three enzymes in the above-named conditions are not in keeping with the pattern seen in myocardial infarction. Angina is not usually associated with an elevated enzyme activity.

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Postpericardiotomy Syndrome Following Penetrating Stab Wounds of the Chest: Comparison With the Postcommissurotomy Syndrome

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The surgery of rheumatic heart disease has drawn attention to a puzzling postoperative complication, usually referred to as the "postcommissurotomy syndrome" (PCS). We report here an identical complication occurring after penetrating stab wounds of the chest, and compare the clinical features with those of the PCS.

The PCS occurs in 10 to 40 per cent of patients after mitral valve surgery. The characteristic clinical features are the presence of pleuropericardial pain, pyrexia, and a tendency to relapse. The pyrexia may be continuous with that of the immediate postoperative period or may appear several weeks or months after the operation. The pain is usually a deep-seated and constricting precordial pain, sometimes sharp, and may radiate to the epigastrium, shoulders, and back. It is often aggravated by changes in posture and by inspiration. Muscle and joint pains may occur, but true arthritis is rare. A pericardial friction rub is commonly heard, and pleural and pericardial effusions may be present. Radiologic examination may show enlargement of the cardiac contour due to pericardial effusion, and the presence of unilateral or bilateral pleural effusions. The electrocardiogram often shows the changes of acute pericarditis. The laboratory findings are not specific, but it is common to find neutrophilia and normocytic normochromic anemia. Transient eosinophilia may occur.[1] The erythrocyte sedimentation rate is invariably raised. The serum antistreptolysin-O titer remains normal. Pleural and pericardial effusions are sterile. Patients seldom appear ill, and there is often a marked disparity between the symptoms and signs and the slight constitutional disturbance. The course is benign. Fever and clinical signs usually subside after a variable period ranging from a few days to several weeks, but may recur, sometimes on several occasions. The condition responds to steroid hormones but not to antibiotics or salicylates.[1,2]

An identical syndrome may follow cardiac surgery for nonrheumatic heart disease. Ito and associates[3] observed this postoperative complication in 13 of 24

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patients with congenital heart disease. In most of these patients the syndrome followed pulmonary valvotomy, although it occurred after surgery for other congenital defects as well. Four of these patients had a pericardial exploration only, without an incision into the heart. When the pericardial cavity was not entered, the syndrome was not observed. Milstein and Brock[4] have described a similar syndrome during the second and third weeks after pulmonary valvotomy; Bedford and associates[5] noted the syndrome after closure of atrial septal defects, and Cooley[6] observed it after operations on ventricular septal defects.

The following are the reports of 2 patients who developed a "pleuropericarditis" after suffering penetrating stab wounds of the chest. A striking similarity to the postcommissurotomy syndrome was observed. Although the occurrence of such a syndrome following cardiac trauma has previously been described,[7-9] this complication has not been sufficiently emphasized in the literature.

CASE REPORTS

CASE 1.—A South African Bantu male, aged 20 years, was first admitted to the surgical unit of Baragwanath Hospital on May 11, 1957, with a penetrating stab wound of the chest. A laceration 1 inch in length was present in the third intercostal space at the right sternal border. A large right-sided hemothorax (Fig. 1,*A*) was aspirated on the fourth hospital day, and 1,100 ml. of grossly hemorrhagic fluid withdrawn. Recovery was uneventful and the patient was discharged after 11 days in hospital.

He was not seen again until 3 months later, when he was readmitted complaining of pain of sudden onset in the chest and epigastrium. The pain was severe and was aggravated by coughing and breathing. On examination he was found to be distressed and in obvious pain. The temperature was 100°F.; the pulse rate was 110 per minute; and the blood pressure was 130/110 mm. Hg. Physical examination was otherwise normal. The next day a pericardial friction rub was heard along the left sternal border and base of the heart. X-ray of the chest showed enlargement of the cardiac shadow and pleural thickening at the right base. An electrocardiogram showed the changes of pericarditis (Fig. 2,*A*).

The patient improved rapidly on symptomatic therapy, and after a week he was apyrexial and the pericardial friction rub had disappeared. He was discharged free of symptoms after 9 days in hospital.

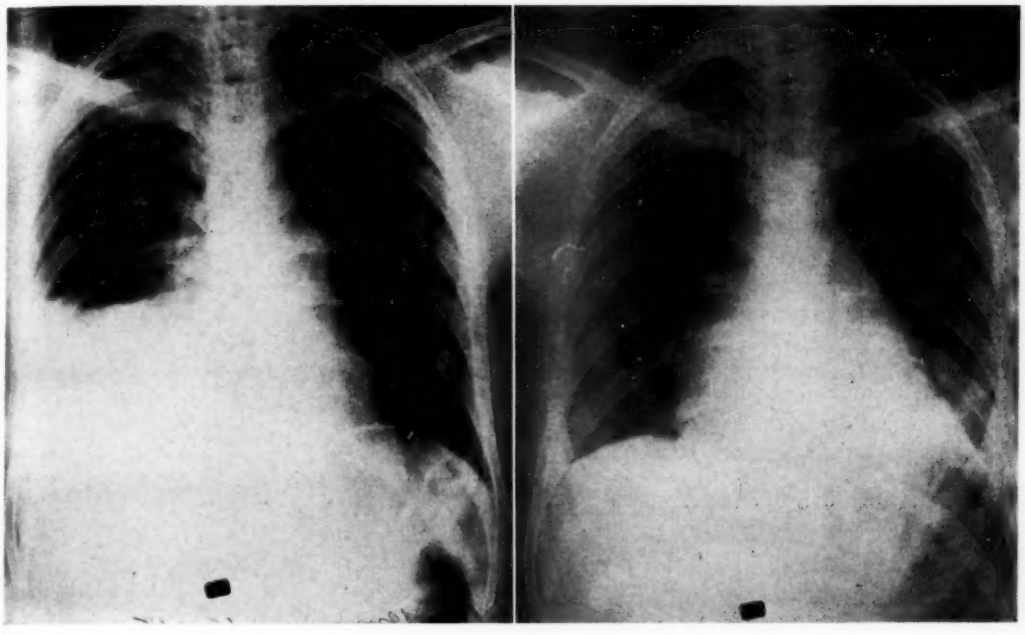
A week later he was readmitted with pleuritic pain in the left side of the chest. On examination a left pleural effusion was found to be present. Increased cardiac dullness and pulsus paradoxus suggested a pericardial effusion. Radiologic examination and fluoroscopy confirmed the pericardial and pleural effusions (Fig. 1,*B*). Aspiration was not performed. An electrocardiogram showed further inversion of the T waves (Fig. 2,*B*).

Irregular fever up to 101.4°F. persisted for 7 days. Recovery again occurred without any specific therapy. The heart shadow returned to normal size within a week, and the pleural effusion cleared (Fig. 1,*C*). The patient has since remained well.

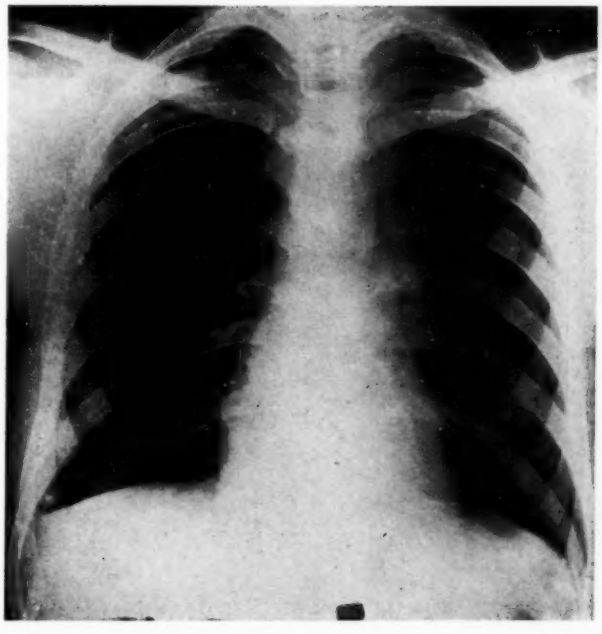
CASE 2.—A 28-year-old South African Bantu male was admitted on June 17, 1956, with a stab wound of the left side of the chest. The wound was situated in the fourth left intercostal space 1½ inches from the midline. The patient was in shock and anemic. Blood pressure was 60/40 mm. Hg. The heart sounds were normal in intensity. Cardiac dullness was not increased, there was no subcutaneous emphysema, and a pericardial friction rub was not heard.

He was transfused with 3 pints of blood and responded satisfactorily. A chest radiograph (Fig 3,*A*) revealed moderate cardiac enlargement (cardiothoracic ratio, 60 per cent), and an electrocardiogram showed marked elevation of the S-T segment in both anterior and posterior leads (Fig. 4,*A*).

The temperature rose to 101.4°F. on the next day and remained elevated for 4 days. After 7 days in hospital the patient was discharged. At this stage he felt well, was afebrile, and showed no abnormality on physical examination, although electrocardiographic changes were still present.



A. *B.*



C.

Fig. 1.—Case 1. *A*, Posteroanterior roentgenogram of the chest on May 13, 1957, showing right-sided hemothorax. *B*, Chest film on Sept. 11, 1957, showing moderate cardiac enlargement (cardiothoracic ratio, 60 per cent), left-sided pleural effusion, and pleural thickening at the right costophrenic angle. *C*, Sept. 24, 1957. The heart size is now normal and the left pleural effusion has resolved.

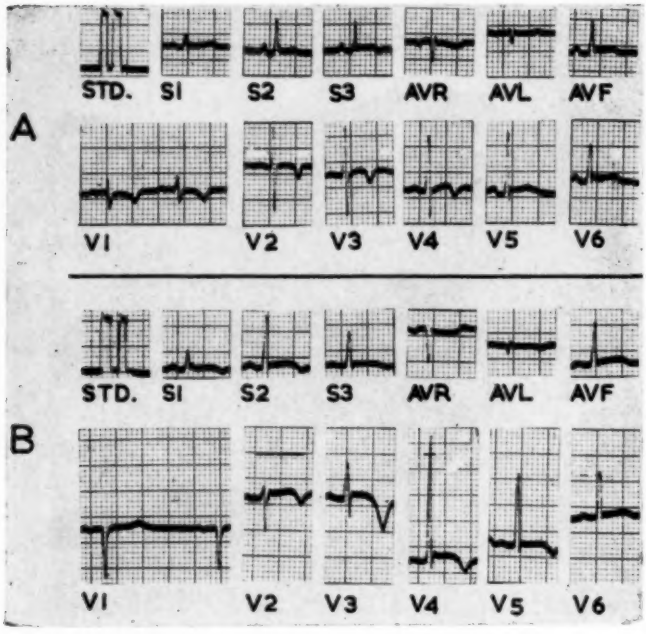


Fig. 2.—Case 1. *A*, Electrocardiogram on Aug. 29, 1957, showing changes of pericarditis. *B*, Sept. 11, 1957, showing deepening of T waves.

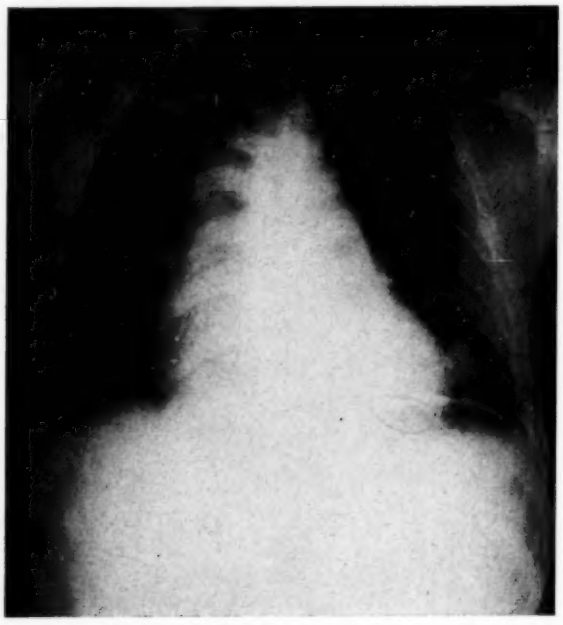


Fig. 3,*A*.

Fig. 3.—Case 2. *A*, Posteroanterior roentgenogram of the chest on June 20, 1956, showing moderate cardiac enlargement (cardiothoracic ratio, 60 per cent). *B*, Aug. 18, 1956. The heart has increased considerably in size. *C*, Jan. 8, 1958. The heart shadow is smaller (cardiothoracic ratio, 51 per cent). (See opposite page for *B* and *C*.)

He was seen again 30 days later, complaining of headache, dizziness, and substernal pain aggravated by movement. Symptoms had been present for 1 week. During the preceding fortnight he had felt quite well. On examination he was found to be febrile (temperature 101.8°F.) and anemic. Pulse rate was 104 per minute; blood pressure was 95/50 mm. Hg, with pulsus paradoxus. The jugular venous pressure was slightly elevated, and the liver edge was palpable. A soft pericardial friction rub was heard at the lower left sternal border, and there were signs of pericardial effusion. The patient did not appear ill in spite of the anemia and fever.

Laboratory investigations showed a hemoglobin of 9.2 Gm. per 100 ml.; white blood cells, 9,500 per cubic millimeter with 80 per cent neutrophils; erythrocyte sedimentation rate, 61 mm. per hour (Wintrobe); C-reactive protein, three plus (+++) positive; serum mucoproteins, 367 mg. per 100 ml.; antistreptolysin-O titer, 50 units per c.c. The Wassermann reaction was negative.

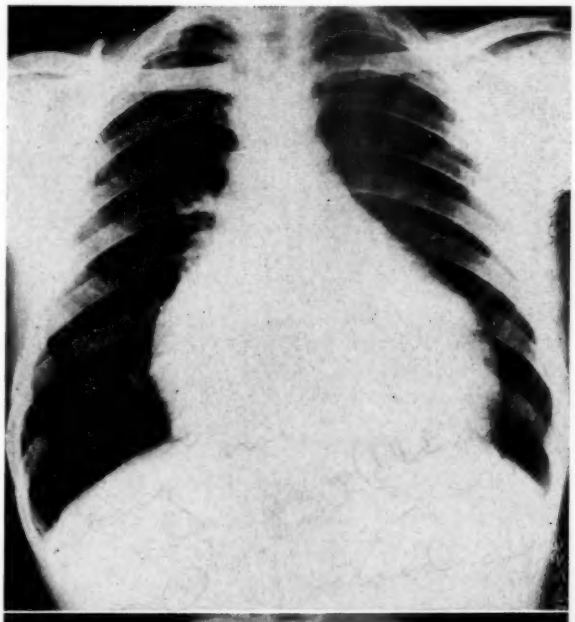


Fig. 3,*B*.

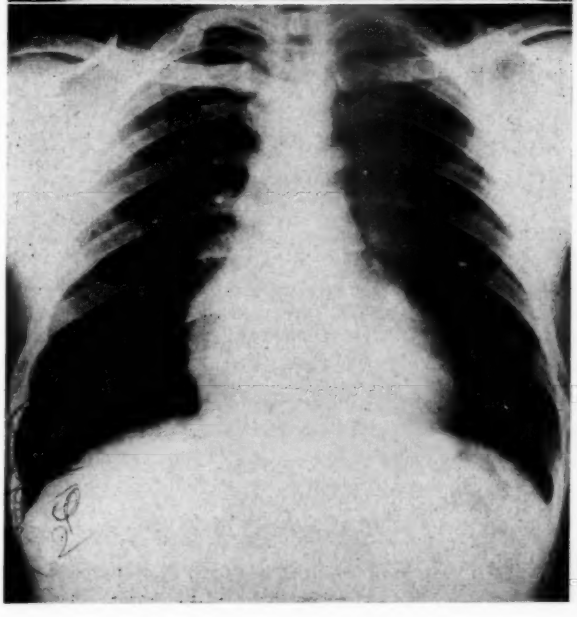


Fig. 3,*C*.

The electrocardiogram showed inverted or biphasic T waves, but the S-T segment elevation which had been so prominent a feature of the initial tracing was now slight (Fig. 4,*B*). Chest fluoroscopy showed a markedly enlarged cardiac shadow (cardiothoracic ratio, 66 per cent) with considerable diminution in the amplitude of the cardiac pulsations (Fig. 3,*B*).

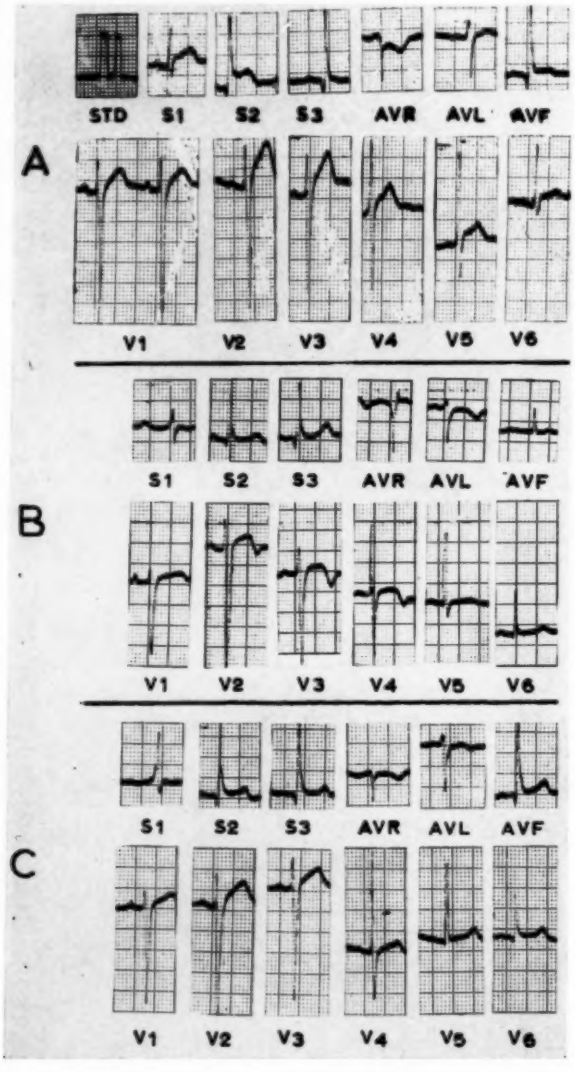


Fig. 4.—Case 2. *A*, Electrocardiogram on June 20, 1956, showing marked elevation of S-T segments in anterior and posterior leads. *B*, Aug. 18, 1956. Elevation of S-T segments is less pronounced and the T waves are inverted or biphasic. *C*, Jan. 8, 1958. The changes of pericarditis are regressing.

Needle aspiration of the pericardial cavity yielded 20 ml. of heavily blood-stained fluid. The fluid was aspirated with difficulty and appeared to be loculated. Analysis of the aspirate revealed the presence of numerous lymphocytes, a few polymorphonuclear leukocytes and serosal cells, specific gravity 1.021, and total protein content 5.3 Gm. per cent. Organisms were not cultured.

Intermittent pyrexia ranging from 99°F. to 102°F. was observed for a period of 23 days. Despite the fever he complained very little and did not look ill. The pericardial friction rub became more pronounced during the first week in hospital and disappeared after 3 weeks. The cardiac

silhouette gradually diminished in size (Fig. 3,*C*), and the electrocardiographic changes slowly regressed (Fig. 4,*C*). He was treated with streptomycin and isonicotinic acid hydrazide for a period of 10 days, without effect on the temperature. Antibiotic therapy was withdrawn when the true nature of the pericarditis became apparent.

At the time of discharge (Aug. 30, 1956) the blood pressure was 130/80 mm. Hg, there were no signs of cardiac tamponade, the hemoglobin was 16 Gm. per 100 ml., and the erythrocyte sedimentation rate, C-reactive protein and mucroprotein values were normal. He has remained perfectly well over a 30-month period of observation

DISCUSSION

Although the course of these two patients differed, the striking resemblance to the PCS is evident in both instances. Case 1 developed the syndrome of pleuropericarditis 3 months after the initial trauma. Of particular interest in this case was the late development of a left-sided pleural effusion following an injury to the right lung. This effusion presumably resulted from contiguity with the pathologic process affecting the pericardium. The symptoms and signs improved spontaneously and showed the characteristic tendency to relapse.

In Case 2 the syndrome appeared 3 weeks after the stab wound, having been preceded by a short period of apparent good health. It then presented as an accentuation and prolongation of the normal course of a stab wound into the pericardium. This course of events is well recognized in the PCS.[10] It can be argued that this mode of presentation may represent delayed hemorrhage into the pericardium.[11] Such an explanation is considered unlikely in view of the difficulty experienced in aspirating the pericardium, and the unusually prolonged course of the febrile reaction. Local experience of delayed hemorrhage following stab wounds of the heart suggests that this serious complication follows an entirely different course from that demonstrated by this patient.[12]

Many hypotheses have been advanced for the pathogenesis of the PCS. Soloff and associates[13] favored rheumatic reactivation as a result of surgical trauma. Verheugt and associates[14] and Fell and Hellman,[15] among others, lent support to this view. However, the absence of preceding streptococcal infection and lack of response to salicylates are factors against a diagnosis of rheumatic reactivation. Serologic tests do not support a rheumatic origin, and there has been no correlation of this complication with the presence of Aschoff nodules in biopsied atrial appendages.[16,17] McAllister[18] suggested infection of the lingula as a possible cause of the PCS.

The most likely and acceptable theory is that of surgical trauma.[10,16,19] The syndrome probably represents a traumatic pericarditis, most likely due to a reaction to blood in the pericardial cavity. The occurrence of this postoperative complication in nonrheumatic subjects argues strongly against the rheumatic nature of the syndrome. The feature common to all these surgical procedures is an incision of the pericardium. Valvotomy, cardiotomy, and injury to cardiac muscle are not responsible factors, because the syndrome may occur when only a pericardiotomy has been performed.[3] The occurrence of this syndrome in our 2 patients following penetrating stab wounds of the chest is a compelling argument in support of the theory that the PCS represents a traumatic pericarditis. Ito

and associates[3] suggest the term "postpericardiotomy syndrome" in preference to "postcommissurotomy syndrome," and it would seem reasonable to designate the syndrome by that name.

Other nonsurgical syndromes which show a striking similarity to the postpericardiotomy syndrome are acute benign relapsing pericarditis[20] and the pleuropericarditis which sometimes complicates myocardial infarction.[21,22] The clinical triad of pleuritis, pericarditis, and pneumonitis is characteristic of this group, as are the frequent relapses. Dressler[21,22] suggests that in myocardial infarction the lesion may act in a manner analogous to that of trauma or surgery, possibly by release of autogenous antigens which cause a hypersensitivity reaction in predisposed persons. The dramatic response to adrenal corticosteroids[23] is thought to support the view that there is an immunologic hyperreactivity in these patients.

Despite the tendency to frequent recurrences, the postpericardiotomy syndrome tends to be self-limited and the prognosis is good. A late complication of hemorrhage into the pericardial cavity may be the development of constrictive pericarditis. This has been reported as a sequel to hemopericardium complicating anticoagulant therapy[24] and following nonpenetrating chest trauma[25-27] as well as penetrating wounds of the chest,[28] and has been produced experimentally by intrapericardial injection of blood and blood lipids.[29]

SUMMARY

Two cases of penetrating stab wounds of the chest are described, complicated by pyrexia, pericarditis, and a tendency to relapse.

The clinical picture is compared with that seen in the postcommissurotomy syndrome. Current views on the pathogenesis of the postcommissurotomy syndrome are discussed.

The striking similarity of traumatic pericarditis to the postcommissurotomy syndrome as well as to the syndrome following surgery of nonrheumatic heart disease suggests acceptance of the more generic term "postpericardiotomy syndrome."

We wish to thank Mr. C. Shevitz for the photographs, Dr. M. Zion for his helpful criticism, and Dr. I. Frack, Superintendent, Baragwanath Hospital, and Dr. E. N. Popper for permission to report these cases.

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Staphylococcal Endocarditis

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Staphylococcal infections and their septic complications have become such a major medical problem that a "Conference on Staphylococci Infections in the Hospital and Community" was convened in Cleveland in 1957.[1] The participants of this conference strongly recommended that every hospital establish a committee charged with investigation and control of staphylococcal infections. They also encouraged bacterial studies and research into the epidemiology, pathogenesis, and therapeutic approach to prevention and control of this serious infection. Just a short decade ago, staphylococcic endocarditis, one of the septic complications, was considered to be an unusual type of bacterial involvement of the cardiac valves. Since 1952, however, it has been increasing in frequency at an alarming rate. Concomitantly, with the increase in frequency of this disease, there has been a rise in the mortality and morbidity associated with the infection.

The development of organisms resistant to the commonly used antibiotics has created a serious problem in the management of disease. Therefore, a review has been made of all cases of bacterial endocarditis due to staphylococcus during the 10-year period 1949 to 1958 in this hospital. A survey of the entire problem of staphylococcal bacterial endocarditis is presented, with emphasis on diagnosis, clinical course, and drug therapy.

METHOD

A search was made of the records of the Bacteriology Department of Hahnemann Medical College and Hospital, Philadelphia, Pa., from the years 1949 to 1958. Charts of all patients who had two or more positive blood cultures for *Micrococcus pyogenes* were carefully reviewed, and only those of patients with definite evidence of bacterial endocarditis were utilized in this series.

The presenting complaints and the etiological, anatomical, and functional types of heart disease were recorded. In addition, note was made of changes in auscultatory findings, onset of congestive heart failure, and the duration of elevation in temperature before treatment was instituted. Embolization was categorized as to site, i.e., brain, kidney, lung, spleen, or extremities.

Laboratory studies included: hemogram, blood urea nitrogen, sedimentation rate, urinalysis, and blood cultures. Staphylococcus organisms cultured were classified as either coagulase positive or negative, and according to their sensitivities.

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If cardiac surgery was done, the type of surgery and the interval of time for development of bacterial endocarditis were then recorded. If death ensued, autopsy findings were included. A complete review of the therapy used and its effectiveness were also evaluated.

RESULTS

Age and Sex.—There was a total of 38 patients, consisting of 22 males and 16 females. The ages ranged from 2½ to 70 years, with a mean of 37 years.

Type of Heart Disease.—The antecedent heart disease in 31 patients was rheumatic in origin, with the number of men and women being approximately equal. Of these, 17 had only the mitral valve involved, 6 had involvement of the aortic valve alone, and 10 had combined aortic and mitral valvular disease. There were 5 individuals with congenital heart disease, consisting of Ebstein's malformation, interventricular septal defect, interatrial septal defect, aortic stenosis, and combined aortic stenosis with coarctation of the aorta.

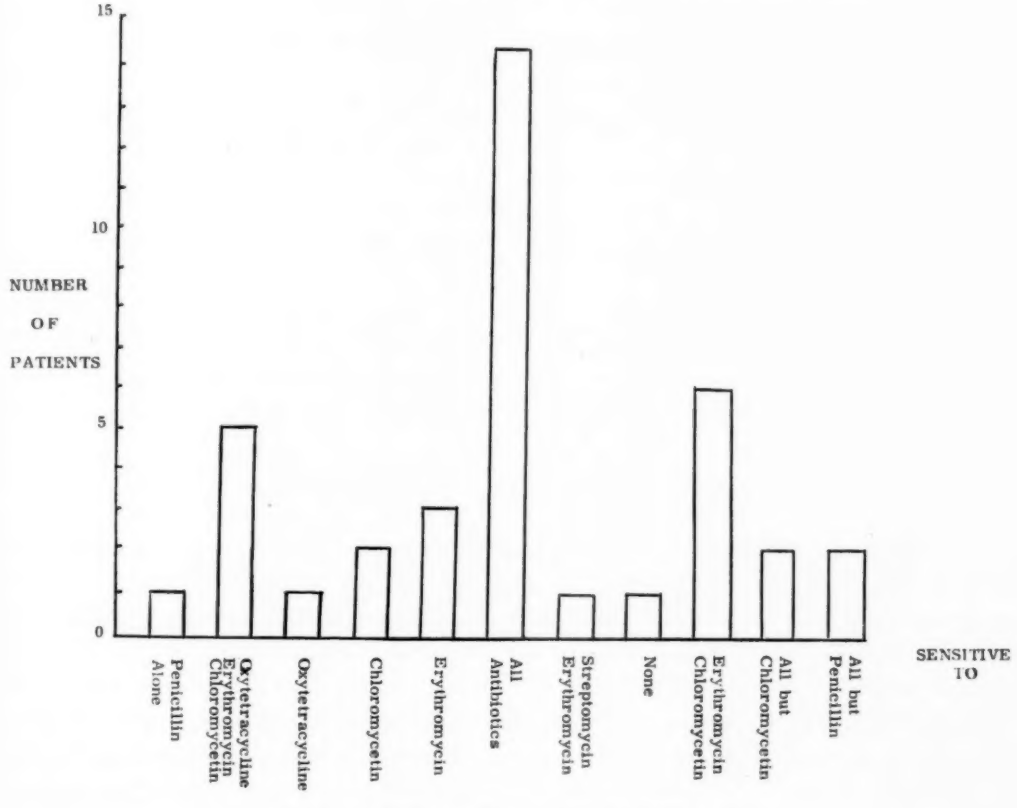

Fig. 1.—Sensitivity of organisms to antibiotics.

Previous Cardiac Surgery.—There were 21 patients who had had previous cardiac surgery, 7 of whom developed staphylococcal endocarditis immediately postoperatively; 11 others developed it within 4 months, and the remaining 3 within 1 year. In all but 2 of these patients the surgical procedures were for correction of rheumatic valvular disease. Among the group with congenital heart disease, there was an aortic commissurotomy for correction of a congenital

aortic stenosis, and a resection of the right atrium for aneurysmal dilatation of that chamber associated with Ebstein's malformation.

Clinical Course.—Fever was present in each of the patients and was the presenting complaint in all but 3 of them. The chief complaint in 1 of these 3 was vomiting and diarrhea, whereas 2 patients had classic congestive heart failure as the predominant presenting symptomatology. Symptoms usually associated with fever, such as chills, night sweats, malaise, and vague myalgias, were commonly present.

Changing heart murmurs occurred in only 3 patients. Congestive heart failure, for the first time, developed in 10 patients during their hospital stay. There were 4 incidents of embolization. One patient had multiple emboli to the brain, left kidney, and spleen; another had emboli to the brain and left posterior tibial artery, and the other 2 patients had emboli to the lungs and left kidney.

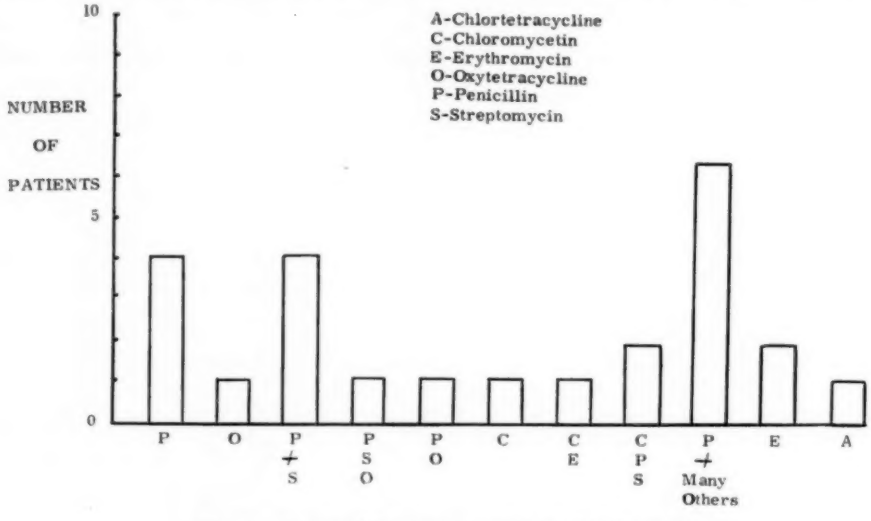

Fig. 2.—Successful treatment and antibiotics used.

Laboratory Studies.—Laboratory studies revealed a leukocytosis in 9 patients, ranging from a total white blood cell count of 12,000 to 24,100 per cu. mm., with a predominance of polymorphonuclear cells. The remaining patients had counts of 4,700 to 11,000 per cu. mm., usually with a normal differential count. The sedimentation rates were elevated (27 to 52 mm. per hour) in 13 patients. The hematocrits were considered to be within normal limits for all except 1 patient who had a hematocrit of 29 per cent. This patient's severe anemia was produced by a chronic brain abscess secondary to multiple septic emboli. The same patient had the only elevated blood urea nitrogen, also the result of renal septic embolization.

Urinalyses were compatible with the usual findings associated with the febrile state, such as mild and transient albuminuria.

Staphylococcus coagulase-negative bacteria were cultured at least twice from the blood of 29 patients, whereas the remaining 9 patients had coagulase-positive organisms. Bacterial sensitivity tests were done by the disk method, with the results shown in Fig. 1. Among the coagulase-negative staphylococci,

40 per cent (14) were very sensitive to all antibiotics, in contrast to only 11 per cent (1) of the coagulase-positive organisms. There was one coagulase-negative bacterium that was resistant to all the usual antibiotics used in the disk method.

Therapy.—Penicillin by intramuscular or intravenous routes was used initially in most of the patients. The dosages ranged from 100,000 to 50,000,000 units per day. When the organism was identified (disk method) and the in vitro sensitivity determined, appropriate changes were made in therapy. In 5 patients, wide-spectrum antibiotics (chlortetracycline, oxytetracycline, or Chloromycetin) were started because the organisms were sensitive only to these drugs and resistant to all others.

The duration of fever before treatment was started varied from less than 24 hours to as long as 4 months. More than half of the patients (22) were on antibiotic therapy within 1 week after the onset of their fever. In those who recovered, fever fell either immediately following institution of therapy or after periods ranging up to 30 days. Two patients with elevations in temperature persisting between 80 and 90 days recovered after surgical removal of their focus of infection. In one case, this was a nylon prosthesis, inserted for the correction of aortic insufficiency; and in the other case, removal of a septic aneurysm from the posterior tibial artery initiated recovery.

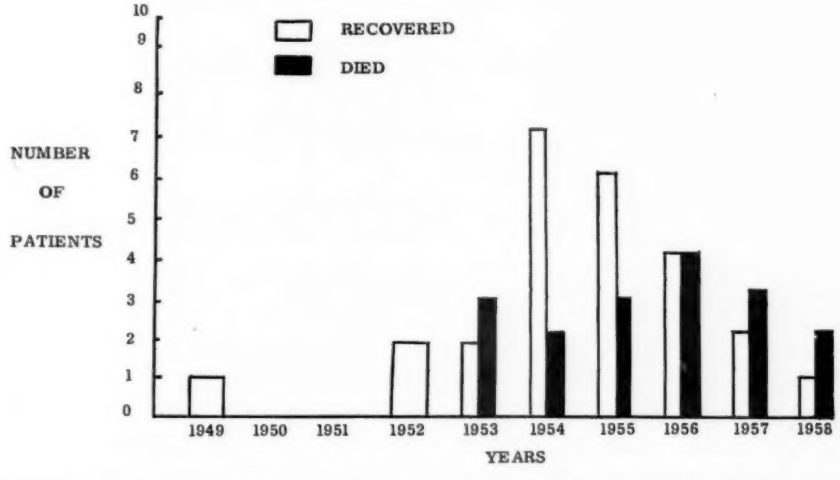

Fig. 3.—Incidence, mortality, and recovery rates in relation to years.

Penicillin alone in doses of 4,000,000 to 30,000,000 units per day was used successfully in 4 patients. Penicillin in doses of 4,000,000 to 50,000,000 units per day combined with streptomycin in doses of 1 Gm. per day resulted in 5 more recoveries. Tetrachlorcycline, oxytetracycline, and Chloromycetin used singly accounted for 3 recoveries. The remainder of the patients who were cured received combinations of several antibiotics (Fig. 2). Penicillin alone or in combination with other drugs was successful in curing 67 per cent (16) of those who recovered (Fig. 2).

Mortality.—The over-all mortality in this series was 37 per cent (14 deaths). Of 17 patients with mitral valvular disease alone, 5 died; of 9 patients with combined aortic and mitral valvular disease, 3 died; and of 6 with aortic lesions alone,

4 died. Death occurred within 9 to 62 days after the diagnosis of bacterial endocarditis had been made and therapy started. In 2 cases the diagnosis was made only upon postmortem examination.

There was a total of 8 cases of staphylococcal bacterial endocarditis from 1949 to 1953, with 5 recoveries. In 1954, there were 9 cases and 7 recoveries, whereas in 1955, there were 9 cases with 6 recoveries. In 1956, 8 cases were treated, with 4 recoveries and 4 deaths. In contrast to previous years, there were 5 cases in 1957, with 3 deaths and 2 recoveries. Only 1 of the 3 cases treated in 1958 survived (Fig. 3). In the entire study, there were 27 patients with coagulase-negative staphylococci, of whom 6 died (23 per cent). On the other hand, between 1953 and 1958, there were 12 patients with staphylococcal coagulase-positive organisms, of whom 8 died (67 per cent) and 4 recovered.

Postmortem Studies.—Autopsies performed on 5 patients (4 with rheumatic heart disease and 1 with interatrial septal defect) revealed typical findings of bacterial endocarditis. Staphylococci were cultured from the involved endocardial areas. All the rheumatic hearts revealed bacterial endocarditis of the mitral valve only. There were septic emboli of other organs in all cases (spleen, kidney, myocardium, brain, and pancreas).

DISCUSSION

The staphylococci are ubiquitous organisms and constitute a major public health problem today. Hospital populations are particularly affected, as manifested by pyoderma neonatorum, mastitis and breast abscess, surgical wound infections, and superimposed infections of debilitated patients. Bacterial endocarditis, likewise, has had a striking alteration in its causative agent, since staphylococcus at present appears to be a more common offending organism than is *Streptococcus viridans.* The source of staphylococcal infections and their mode of spread is a complex problem, and the control of this organism is extremely difficult.[2,3]

This study indicates that cardiac surgery predisposes the valves and endocardium to superimposed staphylococcal infection. It has been postulated that acute endocardial injury produced by the trauma of surgery may be responsible for infection of the normal or chronically diseased endocardium.[4] In addition, the possibility of carriers of staphylococci among personnel in the operating room may also be a factor. The intracardiac use of a bared finger by the surgeon, despite adequate aseptic techniques, will introduce staphylococci. Finally, the resistant strains of staphylococci found in hospitals apparently have a predisposition for the endocardium of postsurgical patients. Among the patients who had had no recent cardiac surgery, only one had definite evidence of a source of the infection. This was due to a staphylococcal mastitis and subsequent abscess formation.

Staphylococcal endocarditis does not present the typical clinical picture of subacute bacterial endocarditis (i.e., *Streptococcus viridans*).[5] There are no splinter hemorrhages, no Osler or Janeway nodes, no petechiae, and usually no enlarged or tender spleen. Likewise, there are no consistent laboratory findings

that would aid in the diagnosis of this infection. Positive diagnosis is made on repeated blood cultures that grow staphylococci. Because of this lack of the characteristic findings of subacute bacterial endocarditis (i.e., *Streptococcus viridans*, enterococcus, etc.), both from a clinical and laboratory standpoint, it is suggested that staphylococcal infection of the endocardium and valves should simply be called staphylococcal endocarditis.

The over-all mortality rate is comparable to that of subacute bacterial endocarditis (30 per cent). More significantly, however, is the prohibitive death rate in the last 5 years: 7 out of 10 patients with this infection failed to recover. There was a significant rise in the incidence of this endocardial complication concomitantly with the general rise in hospital staphylococcal infections. This latter rise is alledgedly due to the development of antibiotic-resistant organisms, a lessening of aseptic techniques, and an increase in human carriers. Increased awareness of this problem, stimulated by the Staphylococcal Infection Committees organized in most hospitals, along with isolation techniques and stringent asepsis has reduced the incidence of staphylococcal endocarditis during 1958 to a low of only 3 cases.

The type of antecedent heart disease was of major importance in determining recovery from staphylococcal endocarditis. All patients with congenital heart disease recovered, except one. These included 3 patients who had developed the infection postoperatively. In striking contrast, 1 out of every 3 patients with rheumatic heart disease died from staphylococcal endocarditis. Also of major importance in recovery were the valve or valves involved. Typically, involvement of the aortic valve alone resulted in death for 2 out of 3 patients afflicted.

Operative procedures within the heart and its major vessels are an important factor in predisposing patients to a staphylococcal infection of the endocardium. This is evidenced by the fact that 2 out of every 3 patients with staphylococcal endocarditis had had previous cardiac surgery. On the other hand, the over-all incidence of staphylococcal endocarditis in patients undergoing cardiac surgery is extremely small. This complication was encountered in only 21 instances out of a total of 3,600 operated cases in the 10-year period of study. Injury to the endocardium produced by surgery, use of a bared finger during surgery, operative contamination, etc., are factors that are probably responsible for the production of this serious infection postoperatively. Although coagulase-negative organisms are considered to be nonpathogenic, they were responsible for 3 out of 5 cases of staphylococcal endocarditis during the 10-year period of study.

A choice of antibiotic cannot be reliably made on "in vitro" sensitivity studies alone. There is little correlation between the disk sensitivity method (more commonly used) and success of the more sensitive antibiotic in curing staphylococcal endocarditis. As a matter of fact, penicillin was found to be ineffective, in vitro, in most cases of staphylococcal endocarditis, yet it produced, alone or in combination, the greatest number of recoveries when used in large doses. Of course, it was the most frequently used antibiotic, and this may be a factor in producing more recoveries. The patient himself is the best "in vitro sensitivity method," and the therapeutic response can be the only reliable yardstick of the proper antibiotic.

Penicillin is still the keystone in the successful treatment of most cases of staphylococcal infection, but, generally, other antibiotics, such as streptomycin, which can be used synergistically with penicillin are required. Those staphylococci which were resistant to the usual antibiotics responded for a short interval of time to the newer agents such as vancomycin, kanamycin, novobiocin, and ristocetin. However, either the toxicity of these antibiotics or the rapid development of resistant organisms quickly diminished the usefulness of these drugs.[6,7]

In contrast to our experience, others have reported favorable results in the use of these drugs in small groups of patients. Vancomycin was used successfully in 4 out of 6 patients by Geraci and his group.[8] However, they encountered toxic effects, consisting of phlebitis, dermatitis, fever, and deafness, in almost all of the patients. Another group apparently cured 7 patients with ristocetin (Spontin),[9] and claims of success for vancomycin and novobiocin also have been published.

The presence of congestive heart failure apparently did not alter the prognosis. Likewise, there was no relationship between the interval of time before treatment was started and recovery. The most significant factor was the removal of any source or focus of the staphylococcus. In one patient, this was a septic aneurysm, and in another it was a nylon prosthesis which apparently harbored staphylococci. Both patients promptly recovered after removal of these foci.

SUMMARY

A review has been made of all cases of staphylococcal endocarditis observed in this hospital in the past 10-year period (1949 to 1958). This study reveals a significant increase in staphylococcal endocarditis in the past 5 years. More significant was the increase in the mortality rate due to lack of response to antibiotic therapy. Cardiac surgery and foci of infections were major predisposing causes for this infection. Successful therapy usually includes penicillin as the most valuable antibiotic.

We wish to thank Dr. Amedeo Bondi, Professor of Bacteriology, for his kind assistance.

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Diagnostic Differentiation of Coexisting Pseudoanginal Root Syndrome and Angina Pectoris

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I. INTRODUCTION

From the early thirties on, several papers have appeared in the U.S.A.[15,18,25,27,32] demonstrating that disease of the cervical spine, by involvement of the sensory nerve roots, was apt to produce angina-like pain; herniated disc,[31] spondylarthritis with osteophyte formation, and/or calcification of the longitudinal and other ligaments of the vertebral column were recognized as the underlying anatomic alterations. Following this pioneer work a number of pertinent studies have been published, culminating in the recent monograph by Davis.[7] Common to these authors is the concept that the pseudoanginal root syndrome—as we may call it—has no relation to true angina pectoris as a manifestation of coronary disease, other than as a source of diagnostic mistake. One may even feel that this interpretation has been stressed beyond the available evidence in case histories in which the reported findings by no means exclude cardiac involvement (e.g., see Reference 32).

In Europe, the interrelationship between spine disease and precordial pain had already been realized at the end of the last century. Following Potain and other, less well-known writers, Huchard,[16] in his outstanding treatise on diseases of the heart (1899-1902), had stressed this point. Not much later, a French neurologist, Lasègue, named the syndrome "angine de poitrine à rebours"; in 1905, at the convention of the French Society for Internal Medicine, Teissier, reporting on rheumatic spine diseases, made the statement: "qu'ils pouvaient aller jusqu'au syndrome d'angine de poitrine" ("that they could enhance the anginal syndrome"). More recently, in a number of papers as well as in monographs, Gallavardin[13] and, later, Lian[20] again insisted on this relation. *Without the instrument of modern electrocardiography, however, and at a time when the pathogenetic definition of angina pectoris as a manifestation of myocardial ischemia had not yet been accepted universally, this early French work remained necessarily vague as a theoretical concept and uncertain in practical diagnosis.*

Starting from this tradition and equipped with the conceptual and instrumental tools of modern cardiology, the cardiological team of Lyons, under

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the leadership of Froment (a pupil of Gallavardin) made, from 1940 onward, a new departure in solving the problem. In several papers[3,10,11] and a recent monograph,[12] they developed the notion of "concatenated" angina (angor intriqué), a term which refers to the true anginal syndrome modified in its symptomatology by a second disease besides coronary sclerosis, e.g., gall-bladder disease, peptic ulcer, involvement of the nervous system, etc. It is true that other authors[1,5,22,24,29,30] have advanced similar ideas, but they considered only the localization of pain, and none of them has devoted a systematic study to all pertinent aspects; and none has collected such a wealth of clinical facts as did Froment and his team.

In the present context, we are concerned only with the influence of coexisting spine disease on the anginal syndrome (called by Froment and his associates "vertebro-coronary concatenation"). When allowance is made for several exceptions, e.g., nocturnal angina ("angine de décubitus"), myocardial infarction, the intermediary syndrome, and the infrequent cases otherwise typical but resistant to nitroglycerin, the following diagnostic rule is valuable for the recognition of "concatenated" angina[11,12]: *Whenever in coronary disease the trigger mechanism producing the anginal attack, its duration, and the site of pain irradiation are atypical, and/or resistance to nitroglycerin is observed, one should suspect and search for coexisting involvement of other organs as the modifying factor.*

Actually, in coronary disease associated with spondylarthritic nerve root compression the anginal pain may be brought about not only by effort, emotion, and cold, as in the usual case, but in the same patient also by bending, by maintaining a sitting or lying position, or by certain movements of the neck and thorax. Therefore, the attacks frequently appear to be spontaneous, especially during the night. After appropriate treatment of the somatic component the attacks initiated by radicular pinching may more or less disappear, but even the spells of effort angina are often notably improved in frequency and intensity, as illustrated by some of the following case reports. Likewise, the unfavorable influence of the somatic component on the duration of effort angina and its reaction to nitroglycerin (to the point of complete resistance) may be established by successful treatment of the spine disease. By these modifications of the anginal attack the clinical similarity to myocardial infarction may become so suggestive that a mistake can be avoided only by instrumental and laboratory investigations.

From the above outline we may conclude that for diagnostic, prognostic, and therapeutic purposes, a comparative study comprising both clinical conditions (pseudoanginal root syndrome and "vertebro-concatenated" angina pectoris) is required, whereas earlier investigators have limited their attention to one or the other aspect of the question.

In a previous paper, we had for the first time insisted on this double aspect of the problem[23]; shortly afterward, Delius[8] expressed very similar considerations. After illustrating the foregoing concepts by two dramatic case reports chosen from a large series, we intend to show in the present paper that both clinical conditions, the pseudoanginal root syndrome and the anginal syndrome associated with and modified by spine disease ("vertebro-concatenated" angina), may coexist in the same patient, and may be distinguished by painstaking clinical analysis.

This special situation will be exemplified by three further case histories. Since the whole weight of evidence lies with the case histories, they will be reported in full detail.

II. CASE HISTORIES

A. *Pseudoanginal Root Syndrome.*—

CASE 1.—Dr. G. B., 1948-57. Electrocardiogram of August, 1957, and fifteen tracings recorded earlier during the years 1942-1957. This case history is of special interest because of the long period covered, the detailed and reliable narration, since the patient was a medical man, and because of the serious psychologic consequences resulting from a mistaken diagnosis maintained over many years.

The patient, today aged 59, a lecturer at a medical school, had his first attack in 1942, while quietly sitting in an armchair; without apparent cause, severe retrosternal oppression with extreme anxiety and cold perspiration supervened and lasted for a quarter of an hour, leaving the patient in a state of profound prostration. After a free interval of more than 2 years, repeated attacks of less severity followed during the spring of 1945. At this time the heart was found to be normal by clinical, radiologic, and electrocardiographic examination. After another year the patient experienced again a number of attacks of slight pain which were of short duration, associated with oppression and dyspnea; they began without apparent cause at rest or during a walk and, in the latter case, did not subside when he interrupted the exertion.

In September, 1954, there was again an extremely heavy attack of oppression and respiratory distress, lasting intermittently for half a day; it was similar in most details to the episode of August, 1957, described below. The patient was urgently rushed to hospital and stayed there for a month, during which time he had repeated attacks, but less severe. Contrary to expectation, body temperature and erythrocyte sedimentation rate showed no change from the normal initial levels, and repeated electrocardiograms were identical with the preceding normal tracings. The precordial area was highly tender to pressure, a phenomenon which later was mistakenly interpreted by a prominent cardiologist as Tietze syndrome. On other occasions the manifestations were considered to be due to coronary disease with secondary cardiac neurosis.

In September, 1955, the patient again had a severe spell of retrosternal pain, when traveling by train; it lasted several hours and was associated with heaviness in the hypochondrium, and belching. The worst attack of the whole illness, however, supervened in August, 1957, and lasted with fluctuating intensity for nearly 24 hours; many spells of agonizing retrosternal oppression, dyspnea, and epigastric pressure, with anxiety and cold perspiration and repeated vomiting followed, one after another. Walking around gave slight relief from the intense suffering. The patient was pale, but the pulse rate and heart sounds were unaltered and the blood pressure showed no consistent change (140-130/90 mm. Hg). Nitroglycerin was completely ineffective, and twice, injections of morphine had to be given. Symptomatically the attack was in no way different from the picture of severe myocardial infarction. But on the following days the leukocyte count (8,200), the erythrocyte sedimentation rate (from the beginning, slightly above normal because of coexisting dental infection), and the normal body temperature remained unchanged; three electrocardiograms recorded during the next 2 weeks were within normal limits, and identical one with the other and also—except for the electrical position—with the numerous preceding tracings (Fig. 1).

During convalescence, the left precordial area, especially the sternocostal junctions, remained tender. Neither by pressure on the vertebrae nor by manipulation of the spine could an attack be elicited. Radiologic examination showed marked cervical spondylarthritis of C_5, C_6, and C_7, with formation of osteophytes, severe alteration of the intervetebral disc C_{6-7}, with narrowing of the intervertebral space, and calcification of the interspinous ligament of the mid-thoracic spine.

On further questioning, the patient finally admitted having suffered for many years from spells of occipital headache; an x-ray film of the cervical spine taken therefor had revealed spondylarthritic changes. But in spite of this finding not one of the physicians consulted, among them eminent cardiologists, had considered its possible relationship with his "anginal" pain. And even now, the patient himself, a victim of professional deformation, could hardly be persuaded that

there was no cardiac infarction and that he was not suffering from coronary disease. Only with difficulty could he be induced to get up and leave the hospital.

Comment.—A 57-year-old physician had suffered for 15 years from attacks of retrosternal oppression, respiratory distress, and epigastric heaviness. He had three attacks of extreme severity, lasting for many hours, refractory to nitroglycerin (as were the less severe spells), and requiring injection of morphine. More than a dozen electrocardiographic tracings, recorded at various intervals

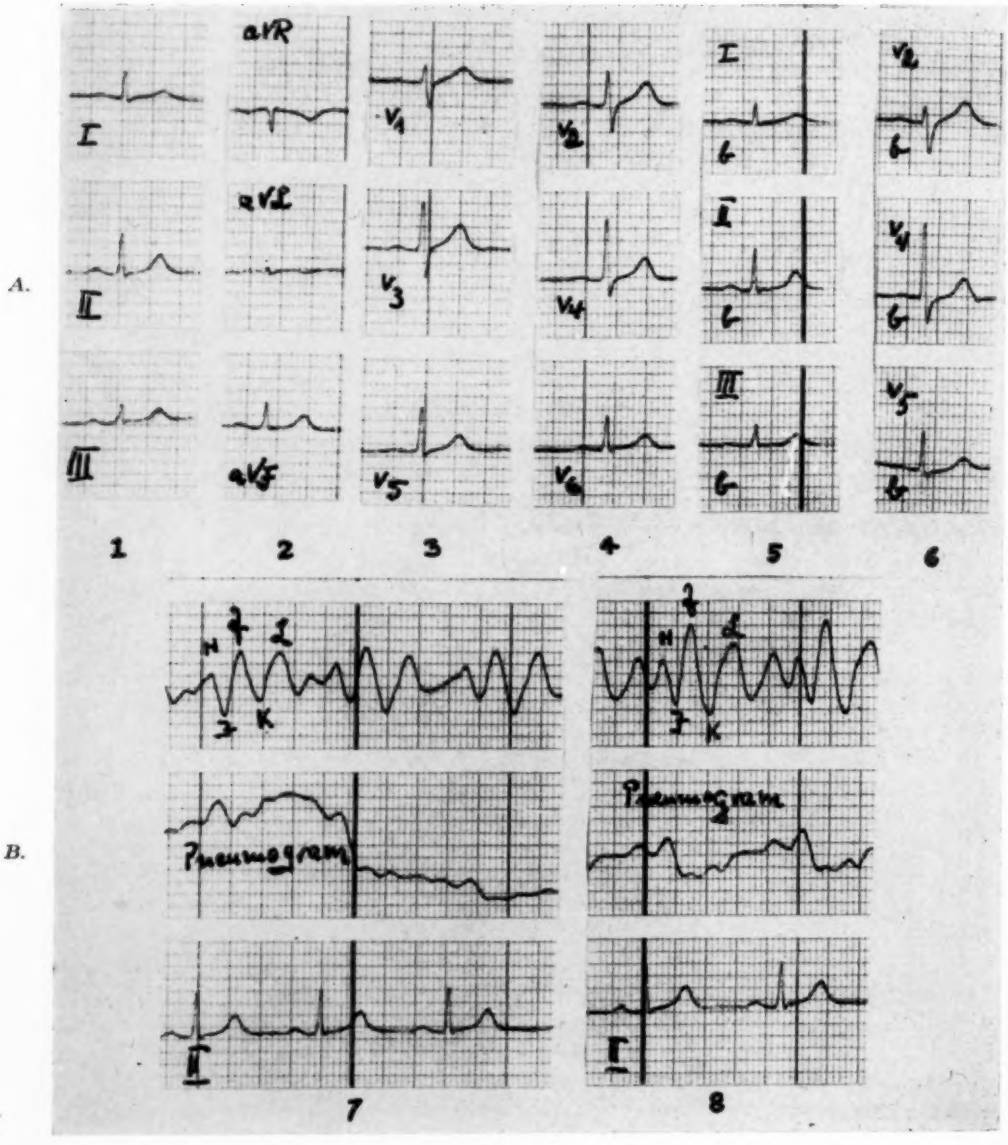

Fig. 1.—ECG and BCG of Dr. G. B. (Case 1), recorded in August, 1957. This tracing was recorded after a 15-year-history of anginal pain with three severe infarct-like attacks, and three weeks after the last of these episodes. There were no significant changes after an exercise test. The BCG was also within normal limits. *A*: *1-4*, ECG at rest; *5*, *6*, ECG after exercise test (climbing 88 stairs). *B:* BCG at rest.

during the long period of observation, were within normal limits and practically without any change of contour during the lapse of years; likewise, there were no suggestive changes in temperature, leukocyte count, sedimentation rate, and blood pressure subsequent to the severe attacks. Nevertheless, seven physicians, among whom were two prominent cardiologists, treated the patient for coronary disease complicated by cardiac neurosis; one made the diagnosis of Tietze syndrome. The presence of spondylarthritis of the spine, however, had been known for many years, since it had also produced suboccipital headache. The mistaken diagnosis of coronary disease maintained for many years had brought about disastrous psychological consequences. Actually, the illness was a typical case of severe pseudoanginal root syndrome.

B. *Angina Pectoris Associated With and Modified by Coexisting Spine Disease (Vertebro-Concatenated "Angina").*—

Case 2.—Mrs. V. T., 1956-59. Six electrocardiograms from January, 1956 to March, 1957. A widow, aged 71, she suffered from many symptoms of autonomic nervous dysregulation, among others from instability of body temperature, with a tendency to hyperthermia during the summer months.

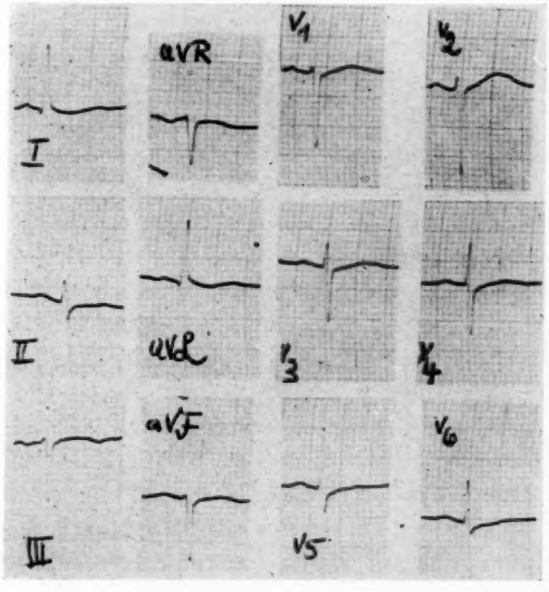

Fig. 2.—ECG of Mrs. V. T. (Case 2) recorded on Aug. 3, 1956; identical with previous tracings. Subsequent tracings showed minimal changes.

From autumn 1955 onward, the patient experienced anginal attacks of ever increasing frequency and intensity, and of a very peculiar symptomatology: pain began usually in the left hypochondrium, progressed gradually to the left lumbar region, the back, the shoulder, the interscapular area, the neck and suboccipital region, the ulnar side of the arm and hand, and culminated in a heavy retrosternal oppression. In minor attacks this typical progression of pain would come to a standstill in any intermediary phase of its development, so that the dysesthesia would remain confined to a more or less limited area. Numerous auricular extrasystoles appeared during the more severe spells. Slight attacks would last from a quarter to a half hour; in the more severe instances the intensity and duration of the pain necessitated the injection of a codethyline preparation, since nitroglycerin had no clear-cut effect.

The beginning of 1956 was marked by the progressive frequency and severity of the attacks; finally, during a whole day, with but short interruptions, a series of severe attacks occurred, occasionally with vomiting. On the following days this anginal state persisted to a lesser extent, accompanied by minimal reactions of leukocytes (7,600→9,900), erythrocyte sedimentation rate (15-22.5 mm.), and temperature (37.8°C.). The ECG was suggestive of chronic coronary disease, but showed neither changes typical of infarction nor, in subsequent tracings, any progression of the initial alterations (Fig. 2). In the following months the frequency of attacks decreased moderately.

During August, 1956, the patient experienced three episodes of tachycardial arrhythmia, with a pulse rate of approximately 160, probably paroxysmal auricular fibrillation, but owing to circumstances not verified electrocardiographically. Early in 1957, the anginal attacks again increased progressively in number and intensity, occurring mostly during the night; finally, in March, the patient once more had an episode of status anginosus very similar to that of the preceding year, but slightly milder; this time also there were only minimal rises in body temperature (37.4°C.) and erythrocyte sedimentation rate (11→17 mm.). Electrocardiographic changes were absent. There remained, however, for several weeks after the attacks a continuous dull pain of fluctuating intensity in the occiput, the neck, and both shoulders. This characteristic feature prompted the radiologic examination of the spine which revealed no cervical spondylarthritis but marked osteoarthritic lipping of the upper dorsal spine: T_{2-3} and T_{5-6}. The cervical spine was also very tender to pressure; it was not possible, however, to elicit an attack by manipulation of the vertebral column.

In view of the radiologic findings, traction treatment of the spine was begun at the end of March, 1957. The result was spectacular. During the following 2 years of observation and up to the present time, only a few slight attacks have occurred. The ECG has remained unchanged.

Comment.—A 71-year-old woman had suffered for 18 months from spontaneous anginal attacks of a very unusual, but stereotyped pain localization. On two occasions an anginal state appeared, with series of attacks interrupted by short intervals, followed by a slight elevation in body temperature and sedimentation rate. The ECG was suggestive of chronic coronary disease, but showed no significant changes during 4 years of observation. Thus, the two major attacks were interpreted as representative of the intermediary syndrome, possibly with minor subendocardial necroses. The second of these episodes was followed by persistent manifestations of a cervical and thoracic root syndrome due to spondylarthritic changes. Manipulation of the spine, however, could elicit no attack. After extension treatment of the vertebral column, both the somatic root syndrome and the anginal attacks disappeared, and the patient has now been free of symptoms for 2 years. The ECG did not change. This case is a striking illustration of how a root syndrome of spinal origin, escaping detection for a long time, may produce, modify, and aggravate the manifestations of otherwise silent coronary disease, and of how treatment of the somatic component may suppress the visceral symptoms without any change in the cardiac state.

C. *Coexisting Pseudoanginal Root Syndrome and "Vertebro-Concatenated" Angina Pectoris.*—The following reports illustrate cases in which the peculiarities of the two syndromes described in Cases 1 and 2 are associated in the same patient, and how they may be differentiated by painstaking clinical analysis.

CASE 3.—Mr. U. P., 1957-1959. Eight electrocardiograms dated from 1944 to 1957. This case report is similar in several respects to Case 1, especially in the mistaken diagnosis which inspired the treatment for many years.

A lawyer, now aged 65, suffered for 14 years from angina-like attacks, often associated with respiratory distress; the pain was localized in the left precordial area. The attacks would occur when the patient was sitting at his desk or, more frequently, during bed rest, rarely during a

walk, when climbing stairs, or after an emotional upset. He stayed repeatedly at an altitude of 2,500 meters (8,000 ft.) and used to make long walks without untoward reactions. Very regularly, however, he experienced attacks when he was holding a small handbag or even a portfolio in the left (but not in the right) hand. These dysesthesias were moderate to severe in intensity and would last several hours, often interfering with sleep. Nitroglycerin was without effect.

Some years ago, the patient had suffered for several months from suboccipital headache, and an x-ray-examination had revealed pronounced cervical spondylarthritis as the causative disorder. Since this finding was discovered during a journey abroad, no further conclusions, diagnostic or therapeutic, were drawn concerning his cardiac status. Actually, during the years 1944-1957, he had been treated by four physicians for coronary disease, although seven electro-

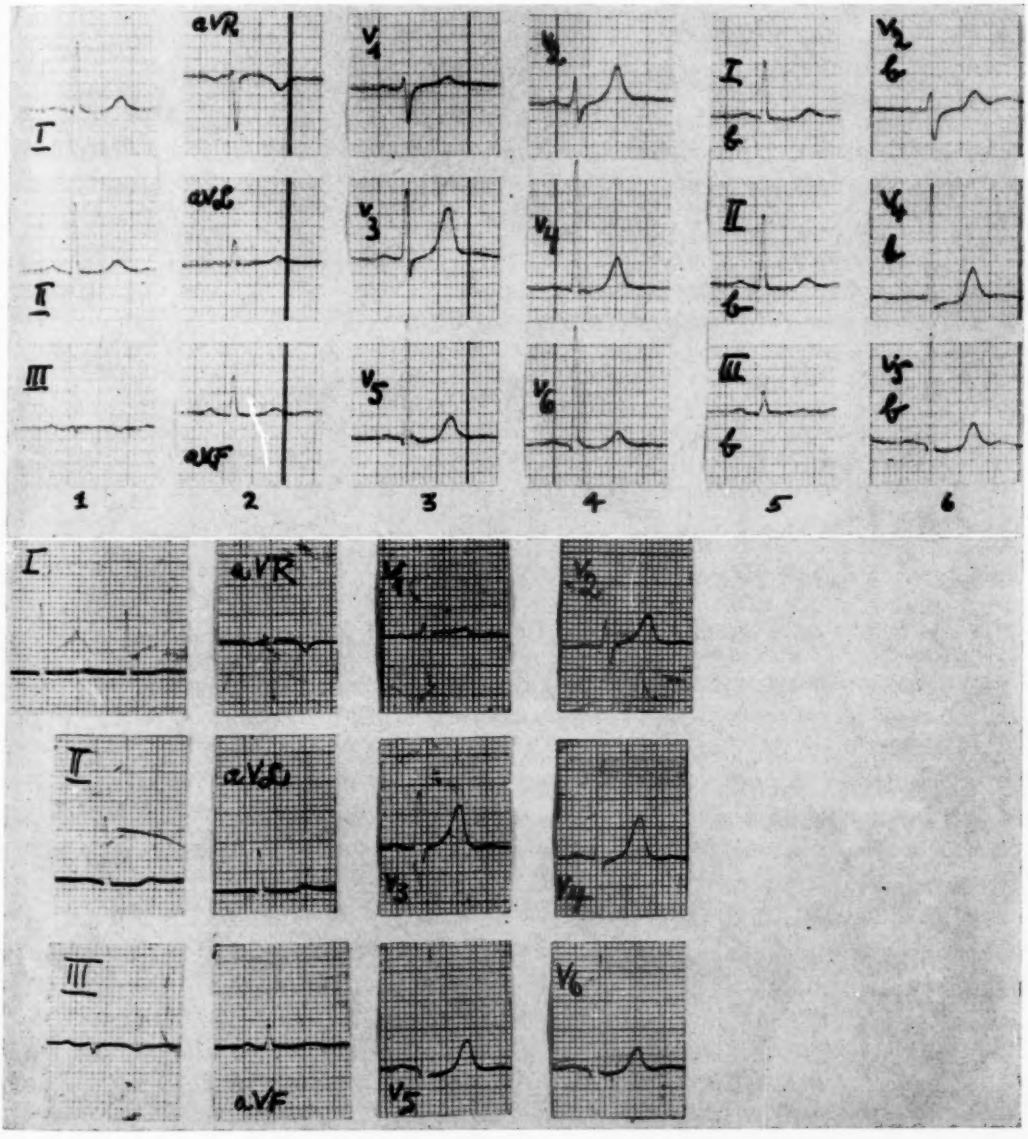

Fig. 3.—Electrocardiograms of Mr. U. P. (Case 3). *A*, ECG recorded in December, 1957, identical with six other tracings recorded between 1944 and 1956; *1-4*, at rest; *5*, *6*, after exercise test (climbing 88 stairs). *B*, ECG recorded in April, 1957.

cardiograms recorded at different times during that period were within normal limits and did not show any change of contour; they were identical with a further tracing taken in December, 1957 (reproduced in Fig. 3), with one exception, which will be discussed below.

Moreover, after an extremely severe nocturnal attack of precordial pain lasting for several hours, which occurred in the spring of 1956, the patient was kept in bed for 1 month, with the diagnosis of myocardial infarction, although changes in body temperature, erythrocyte sedimentation rate, blood pressure, and ECG were absent. Finally, after a similar attack in September, 1957, a new x-ray examination of the spine was performed; it revealed very extensive spondylarthritic changes of nearly the whole vertebral column, showing enormous osteophytes, often with bridging of the intervertebral spaces on their anterior and lateral faces, degeneration of the intervertebral discs, and narrowing of the intervertebral spaces. There was notable arthritis of the small intervertebral articulations. The alterations were most pronounced between C_6 and C_7.

On clinical examination, the spine was very tender to pressure. Furthermore, *a slight "anginal" attack could be elicited with experimental regularity by the manipulation of the spine, e.g., by leftward bending and rotation of the thorax. The sensation tone and localization of the pain were identical with the spontaneous attacks, and very characteristically, the pain did not immediately subside with the return to normal body position.* This clinical experiment represented in itself alone decisive evidence for the vertebral origin of the attacks. Measurements of the cardiac silhouette were within normal limits, but the apex was emerging from the diaphragmatic shadow and was more rounded than usual (see below). Blood pressure was between 150/90 and 160/90 mm. Hg.

Traction of the vertebral column was not effective, but after a series of procaine infiltrations, deep and superficial, of the pain area (corresponding to innervation from C_6 and C_7) the attacks have now been absent for a period of 1½ years.

In 1958, the patient's blood pressure rose on two occasions to hypertensive levels (190-210/90-100 mm. Hg) and was maintained at these levels for 1 to 2 weeks. During these periods, when walking quickly, he experienced true retrosternal oppression, which subsided at rest. These spells were of short duration, their localization and sensation tone were very different from the precordial pain described above, and they were promptly abolished by nitroglycerin. After further questioning, the patient gave the information that he had suffered from similar spells of retrosternal oppression during earlier periods of paroxysmal hypertension. In April, 1957, an ECG had been recorded under such circumstances when the blood pressure had risen to 205/100 mm. Hg. It was the only tracing of the series not identical with the others and was plainly abnormal (Fig. 3). There was low voltage of the T waves in the limb leads, and in L_2 a horizontal S-T segment with the initial leg of T rising in a brisk angle: features suggestive of myocardial ischemia. Probably the peculiar contour of the cardiac apex was also related to the paroxysmal arterial hypertension. With appropriate treatment it was possible to prevent further spells of hypertension and, thereby, the attacks of retrosternal oppression associated with it.

Comment.—A 65-year-old man had suffered for nearly 15 years from attacks of left precordial pain which had been interpreted and treated by four physicians as angina pectoris and, after one episode of special severity and long duration, as myocardial infarction.

The following findings represented demonstrative evidence that the attacks were actually a pseudoanginal root syndrome of vertebral origin: (1) The attacks were not brought about by effort, emotion, or cold and were not influenced by nitroglycerin; their occurrence was not enhanced by meals and high altitude. (2) They appeared mostly during bed rest or when the patient was lifting a small weight with the left (but not with the right) arm. (3) *Pain of the same sensation tone and identical localization could be experimentally produced by enforcing a certain position of the thorax (left bending and rotation).* (4) The ECG tracings remained within normal limits and without any changes during the long observation time of 14 years; even after the severest attacks lasting for several hours the body

temperature, sedimentation rate, and blood pressure showed no alterations. (5) There was extensive severe spondylarthritis of nearly the whole spine, most pronounced at the level of C_6 and C_7.

By a series of procaine infiltrations of the thoracic wall, corresponding to the implicated segments, the syndrome was definitely and—so far as apparent after an observation of $1\frac{1}{2}$ years—permanently cured.

Treatment of visceral pain by procaine infiltration of corresponding surface structures was introduced in the U.S.A. by S. Weiss and Davis[35] and in the same year, 1928, by Lemaire,[19] in France, and has been more recently advocated again by Travell and Rinzler.[29,34] Our own experience in pertinent cases was very satisfactory. However, since anesthesia of the somatic component is often effective in the treatment of referred pain due to visceral disease alone, its favorable influence in the present case is no further argument for the extracardiac origin of the attacks.

More infrequently and exclusively during short periods of transitory arterial hypertension the patient had also attacks of retrosternal oppression. These attacks varied as to the mechanism which brought them about, being always elicited by effort; they also varied in their clinical features, lasting only for a few moments and subsiding at rest; they were strictly retrosternal in localization and had a totally different sensation tone; and finally, they reacted promptly to nitroglycerin. With the successful preventive treatment of the hypertensive periods these attacks disappeared completely. Evidently, these were attacks of true angina.

To conclude, the patient was suffering simultaneously from an anginal root syndrome of vertebral origin and true angina pectoris, conditions which could be distinguished by their respective peculiarities. No causative interrelationship between the two syndromes was apparent in this case.

CASE 4.—Mrs. P. M., 1958-1959. Seven electrocardiograms dating from October, 1958 to April, 1959. A widow, aged 55, sought medical advice for the first time in October, 1958. At that time she had been suffering for nearly 3 months from a continuous sensation of strangulation and anxiety in the pharynx, which after effort became increasingly violent, and was associated with painful retrosternal oppression. She had four to seven attacks during the day and occasionally also during the night. They were always relieved by nitroglycerin. Beside these dysesthesias the patient complained of a different painful sensation, localized in the left precordial area between the mammillary and axillary lines; it appeared also in attacks, but independently of effort, would last for several hours, and was not relieved by nitroglycerin. Finally, she had from time to time "neuralgic" pain of the occiput, irradiating behind the ears, in the neck, the interscapular region, and both shoulders, lasting for many hours and not subsiding after nitroglycerin.

The patient was moderately obese and had a mild diabetes; fasting blood sugar was 113 mg. per cent; it rose to a maximal value of 188 mg. per cent in a test with peroral administration of 50 Gm. of glucose. Serum total cholesterol was 294 mg. per cent. Arterial blood pressure was between 160/110 and 150/100 mm. Hg. The heart was slightly enlarged to the left. Several ECG tracings were recorded in October and November, 1958, at rest and after slight exercise; they showed no significant change (Fig. 4,*A*) during this period.

The tracings recorded in 1958 with the patient at rest showed an ischemia pattern of the ST-T complex most obvious in the chest leads V_1-V_4 and L aVL. The changes were notably intensified by minimal exertion (not illustrated). The electrocardiographic diagnosis was diffuse coronary disease with predominant ischemia of the anterior wall. Conventional treatment with various vasodilator drugs and heparin, continued for 2 months, produced only slight relief.

The radiologic examination of the cervicodorsal spine revealed spondylarthritis involving C_5, C_6, and C_7, with osteophytes projecting from the anterior and posterior corners of the affected vertebrae, and with narrowing of the intervertebral spaces C_{5-6} and C_{6-7}. There was encroachment of osteophytes on the left intervertebral foramina C_{5-6} and C_{6-7}. Pressure on, and manipulation of, the spine and extreme positioning of the neck and thorax did not elicit attacks. But the precordial area, especially the costocartilagineal junctions C_2, C_3, C_4, and C_5, was highly tender to pressure.

The effect of traction of the spine was spectacular, as evidenced by the speed and extent of improvement. The continuous sensation of strangulation and the long-lasting attacks of left precordial pain which were independent of effort and not relieved by nitroglycerin disappeared at once. Initially, the anginal attacks of retrosternal oppression were only improved in frequency (two to four weekly) and intensity, but finally, after repeated orthopedic applications, they became very rare. After 5 months of therapy the patient was practically free of manifestations, cardiac and somatic. Most notably, in accordance with the clinical improvement, there was also a great normalization of the ECG (Fig. 4,*B*). Actually, at rest the ECG showed now the features of a borderline tracing, the negative T waves having completely disappeared; even after moderate exertion the ischemia pattern, still present in the chest leads, was rudimentary: a horizontal S-T segment, followed briskly by a straight-lined ascending leg of T in Leads V_4 and V_5. The ballistocardiogram, however, gave unchanged evidence of the persisting cardiac involvement (Fig. 4,*C*).

Comment.—A 55-year-old diabetic woman had suffered from frequent (four to seven daily) short attacks of severe retrosternal oppression, mostly brought about by effort and relieved by nitroglycerin. Furthermore, besides a continuous sensation of strangulation she complained of left-sided precordial pain, occurring without relation to effort, of long duration, and not relieved by nitroglycerin. Frequently, she had also "neuralgic" pains in the occiput, neck, interscapular area, and both shoulders. The ECG recorded at rest and after slight exertion showed the pattern of pronounced ischemia. X-ray examination of the cervical spine revealed marked spondylarthritis, with encroachment of osteophytes on the intervertebral foramina.

As evident from the foregoing description, the mechanism of precipitation, the localization, and the clinical features and duration and their reaction to nitroglycerin were different for the two types of attacks, and made it possible to attribute the spells of retrosternal oppression to the coronary disease evidenced by the ECG and to identify the left precordial pain as a manifestation of a cervical root syndrome appearing with symptoms of somatic neuralgia and due to the coexisting spondylarthritis.

But, whereas in the preceding observation (Case 3) the anginal attacks were not atypical and did not exhibit the peculiarities of "concatenated" angina, the present patient demonstrated the aggravating and modifying influence of the coexisting root syndrome; this was also obvious in the spectacular effect of orthopedic treatment, which immediately reduced the frequency and intensity of the otherwise therapy-resistant anginal spells. In the absence of other pertinent observations the significance in this context of the improvement of the ECG cannot be conclusively evaluated. Anyhow, improvement of the cardiovascular condition and normalization of the ECG by eradication of an interfering extracardiac disturbance are well in keeping with available clinical experience: in fact, functional and electrocardiographic amelioration of concomitant cardiac involvement is a common observation after surgical cure of chronic gall-bladder disease (References 2, 4, 9, 14, and many others).

CASE 5.—Mr. A. H. Five electrocardiograms from May, 1957 to March, 1959. This 67-year-old man had suffered since 1956 from attacks of pain in the left subclavicular area above the precordium; these attacks lasted for a few minutes and occurred independently of effort and emotion on several occasions when he was quietly sitting in his armchair or lying in bed. A cardiologist made the diagnosis of coronary sclerosis and prescribed vasodilator drugs and, for the emergency,

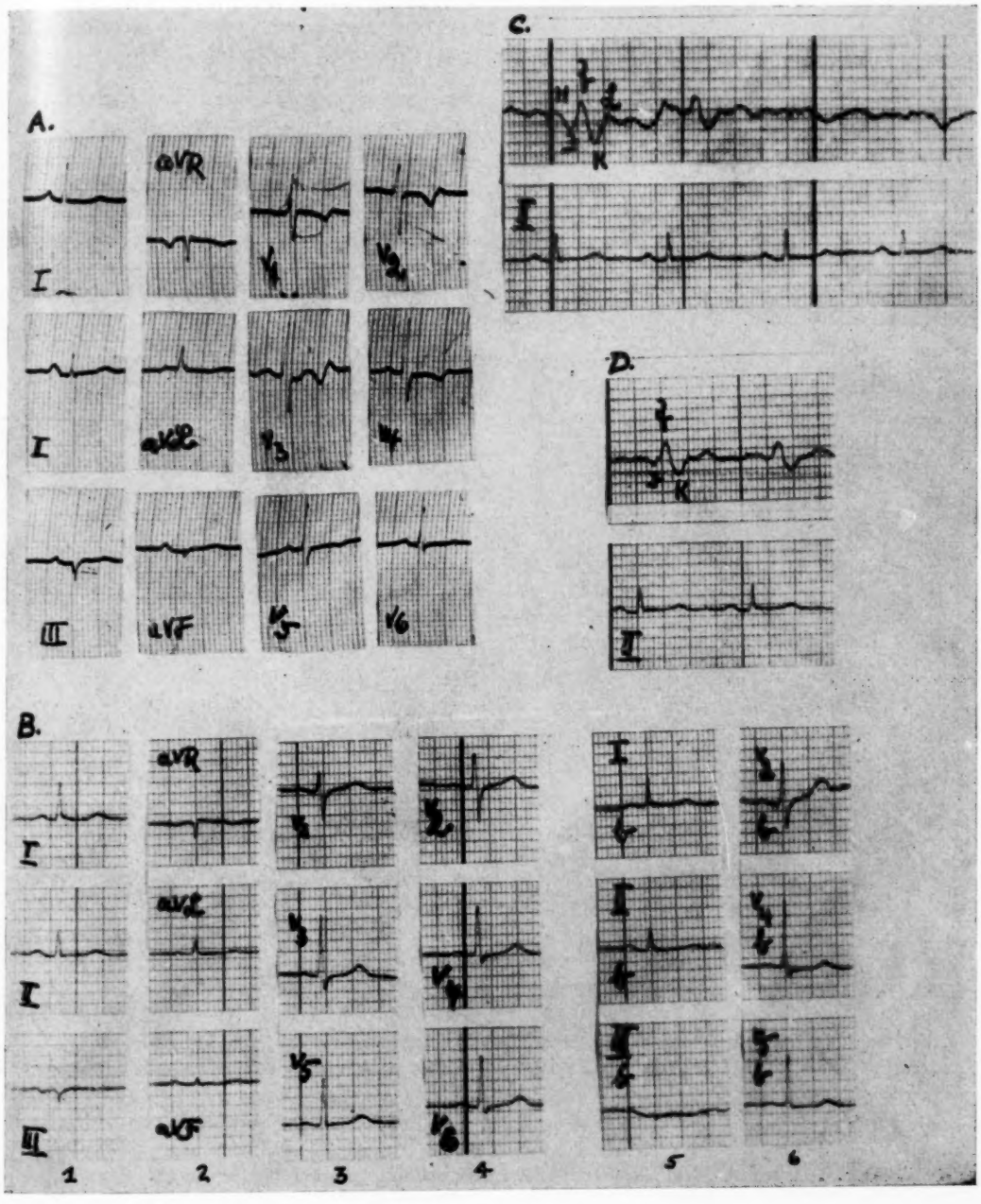

Fig. 4.—Electrocardiograms and ballistocardiograms of Mrs. P. M. (Case 4). *A*, ECG recorded in November, 1958. *B*, ECG recorded in April, 1959; *1-4*, at rest, and *5*, *6*, after exercise test (climbing 22 stairs). *C*, *D*, Ballistocardiograms recorded in April, 1959; *C*, with normal respiration, and *D*, with held respiration.

nitroglycerin tablets, which proved ineffective. Several 12-lead electrocardiograms recorded at rest were within normal limits. Some months later the patient also experienced slight pain localized in the same area and of identical sensation tone when speeding up his walk; this dysesthesia subsided after a few moments of rest and was prevented or quickly relieved by nitroglycerin.

In November, 1958, he suffered again two severe attacks of agonizing pain, of short duration, when sitting with friends at table; nitroglycerin was once more without effect. Firmly convinced that he was badly stricken with heart disease, he sought new medical advice.

He was a robust plethoric man of athletic complexion, moderately obese (weight: 99.0 kilograms; height: 1.76 meters). The blood pressure was between 155/75 and 135/65 mm. Hg; serum total cholesterol, 200 mg. per cent; glycemia, 88 mg. per cent; erythrocytes, 5.0 to 5.5 million; hemoglobin, 14.5 to 15.9 Gm. per cent. The heart sounds were distant, a fact attributed to the existing emphysema. The latter was presumably also to blame for the low voltage of the QRS complex in the limb leads as shown in the tracing recorded in March, 1959 (Fig. 5); otherwise, the resting ECG was within normal limits, but after slight exertion (climbing 88 stairs) the ST-T complex showed moderate changes of the subendocardial ischemia pattern in L II and the left chest leads. In the BCG, abnormalities of degree 2-3 (according to the classification of Brown-DeLalla) were present, hardly a pathologic finding in the patient's age group. Electrocardiograms and ballistocardiograms recorded in December, 1958, and March, 1959, showed no further development.

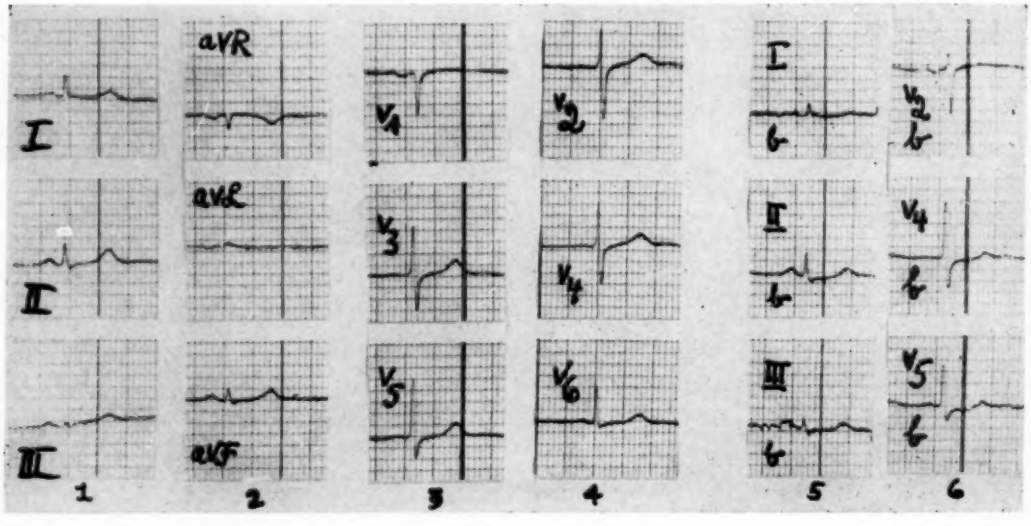

Fig. 5.—Electrocardiogram of Mr. A. H. (Case 5), recorded in March, 1959; *1-4*, at rest, and *5*, *6*, after exercise test (climbing 88 stairs).

The x-ray examination showed marked spondylarthritis of the whole thoracic and lumbar spine, with lipping of the right and left corners of the involved vertebrae and kissing osteophytes projecting laterally and anteriorly, as well as mild calcification of the interspinous ligament, the latter being present also at the level of the cervical vertebral column.

At the time of the physical examination, one outstanding finding was noted. *By manipulation of the cervicodorsal spine (bending and rotation to the left) it was possible to elicit with experimental regularity pain in the left subclavicular area, of the same localization and sensation tone as during the attacks.* After a few procaine infiltrations of this area (superficial and muscular structures) the attacks occurring both at rest and after effort disappeared completely; moreover, it became impossible from the very beginning to elicit the pain by manipulation of the spine.

Comment.—A 67-year-old man had suffered for several years from attacks of pain in the left subclavicular area above the precordial region; they supervened

mostly when the patient was sitting at table, were occasionally of extreme severity, and were never relieved by nitroglycerin. Some years later, he also began to experience slight anginal pain after effort, localized in the same area and of the same sensation tone. These latter attacks, however, subsided quickly at rest and yielded immediately to nitroglycerin. Examination revealed (1) a very slight degree of coronary insufficiency, with a normal resting ECG, but with a faint ischemia pattern of the ST-T complex appearing in some leads after effort, and (2) spondylarthritic changes of the cervicodorsal spine. *By manipulation of the vertebral column the pain could be regularly elicited.* After repeated procaine infiltrations of the area the attacks both at rest and after effort disappeared, and pain could no longer be elicited by manipulation.

This patient illustrates the coexistence of "concatenated" anginal pain of effort and the pseudoanginal root syndrome. The modification of the anginal attacks by the somatic component was manifest in the atypical site of pain, and possibly also by the very presence of effort angina with insignificant coronary disease.

Contrariwise to the two preceding cases (Cases 3 and 4) the pain area of both the visceral anginal and the somatic pseudoanginal syndromes was the same; different, however, were the conditions of manifestation and the reaction to nitroglycerin. The decisive influence of the somatic component was apparent in the experimental production of the pain by means of manipulation of the spine, and in the complete suppression of pain after manipulation and of the attacks by procaine infiltration of the involved area.

III. DISCUSSION

Cases 1 and 2 illustrate by typical and dramatic histories the characteristic features of the pseudoanginal root syndrome due to cervicodorsal spondylarthritis and of vertebro-"concatenated" angina pectoris, respectively; surprisingly enough, to the latter clinical condition the English and American cardiologists have paid hardly any attention.

Very recently, however, we made a comparative study of both syndromes,[23] and the pertinent question of "concatenated" angina has been extensively treated by the Lyons cardiological team.[3,10-12] Hence, this problem will not be commented upon in the present paper.

On the other hand, Cases 3, 4, and 5 illustrate the fact that both conditions may be associated in the same patient, and demonstrate how painstaking analysis may succeed in distinguishing them clinically. The details on which such an analysis is based have been elaborated upon in the foregoing case histories.

In the same patient the pain arising from the pseudoanginal root syndrome and that from the anginal attack may be of different localization and sensation tone (Cases 3 and 4) or may differ only by other peculiarities of symptomatology (relation to body posture and/or effort, duration of the pain, effect of nitroglycerin [Case 5]). By interference of the somatic component the anginal attack may be modified in its features (intensity, duration, reaction to nitroglycerin) (Case 4) or may not (Cases 3 and 5).

For the principles of diagnosis of pertinent pain syndromes we may refer to the introductory exposition. As easily understood, the radiologic evidence of cervical spondylarthritis alone is by no means sufficient for the diagnosis, since these degenerative and productive changes of the spine are increasingly frequent from the age of 40 onward (75 per cent above 40 years[32]; 85 per cent[17]). When pain which is identical in localization and sensation tone to that of the attacks can be elicited experimentally by manipulation of the spine (Cases 3 and 5), a decisive criterion of diagnosis is at hand; but in the majority of cases such provocation is not possible. Success of cervical traction is also a valuable confirmation of diagnosis, but failure is no peremptory counterargument (Case 3). Final diagnostic appreciation, as always, is based on the synopsis of all available facts.

When one takes stock of the syndromes of cardiac pain, as described above, related to cervical spondylarthritis and their various associations reported in the present paper, the following classification can be established: (1) pseudoanginal root syndrome (Case 1); (2) "concatenated" angina pectoris (Case 2); (3) pseudoanginal root syndrome associated with common angina pectoris (Cases 3 and 5); (4) pseudoanginal root syndromes associated with "concatenated" angina (Case 4).

The realization, so often missed, in patients with spondylarthritis that extracardiac factors are enhancing the frequency, duration, and intensity of attacks is of paramount clinical importance, since treatment of these trigger mechanisms may yield spectacular therapeutic results, whereas conventional therapy directed at the circulatory disturbance alone may be completely deceptive (Case 4). Actually, in the reported series of observations the interference of a somatic component was initially not realized in all five cases, a mistake which caused a delay of effective treatment ranging from several weeks to 15 years.

The interaction of the somatic component in angina pectoris can bring about the development of a clinical picture masquerading as myocardial infarction, being well described by the old term "status anginosus"; hence, it is not true, as Nichol and associates[26] would have it, that "status anginosus (not: anginosa) is a hand-me-down term from the days when the difference between angina pectoris and acute myocardial infarction was not appreciated, and there is no reason for retaining this term."

So far as the localization and nature of pertinent vertebral alterations are concerned, the present observations made it possible to relate cardiac pain, anginal or pseudoanginal, definitely to spondylarthritic changes at the level of C_{5-6} down to T_{2-3}. Radiologic findings were accepted as argument for causal relationship only if, by experimental provocation or by the indisputable therapeutic result of extension treatment, the changes present could be evidenced as instrumental for the trigger mechanism of the attack. Although there may be some rough parallelism between the importance of the spine disease, and its potential relation to cardiac pain, this is no general rule; actually, a small osteophyte situated at a strategic point may be more important than major alterations located elsewhere. Furthermore, it is difficult to explain why, in spite of the overwhelming frequency of spondylarthritis in the older age groups, the disease plays only an occasional role in cardiac pain. There is no factual answer to this

crucial question. The difficulty, however, is just the same as in the case of the relationship between coronary disease and anginal pain which has bedeviled this problem for more than a century. In both instances the hypothetical explanation points, in accordance with Libman's[21] classic work on sensibility to pain, to the conditioning influence of the nervous system, both somatic and autonomous.

In pertinent conditions we have obtained good therapeutic results by extension of the spine and/or by procaine infiltration of the somatic pain area. Occasionally, only one or two applications of extension were rewarded by full therapeutic success; more frequently, in other cases a series of applications was needed, and in some patients this treatment met with failure. Results were likewise unpredictable with procaine infiltration. But in not a few cases the results of these therapeutic procedures, both extension and infiltration, were truly startling (Cases 2, 3, 4, and 5).

Some 60 years ago the outstanding French cardiologist Huchard[16] wrote in his textbook on diseases of the heart: . . . "There are not several kinds of angina pectoris, there is one alone, all the other forms being spurious. And if one would not be able to differentiate between the one and the others, I wonder what purpose medical science could serve." Now, very recently, Prinzmetal and associates[28] have distinguished on electrocardiographic criteria two forms of angina; on the other hand, in the present study, from a clinical point of view, three forms are differentiated. Evidently, concepts have changed tremendously since the above phrases were written.

IV. SUMMARY

To the well-known concept of pseudoanginal root syndrome is opposed the notion of "vertebro-concatenated" angina pectoris, as developed by the Lyons cardiological team under the leadership of R. Froment. The aforementioned term means true angina pectoris which, by an associated root syndrome corresponding to the level of cardiac innervation, is modified in its manifestations, e.g., the instrumental trigger mechanism, the localization, duration, and intensity of pain, as well as its reaction to nitroglycerin.

In the present paper the two concepts are illustrated by dramatic case histories. Two case histories illustrate the peculiarities of the pseudoanginal root syndrome and of "vertebro-concatenated" angina respectively. Three further case histories are reported in which the pseudoanginal root syndrome was associated in the same patient with true angina pectoris, either of the common type or of the "vertebro-concatenated" form.

On the basis of these observations, four types of cardiac pain related to cervical spondylarthritis can be distinguished: (1) pseudoanginal root syndrome, (2) "vertebro-concatenated" angina pectoris, (3) pseudoanginal root syndrome associated with common angina pectoris, and (4) pseudoanginal root syndrome associated with "vertebro-concatenated" angina pectoris. The five case histories reported illustrate every aspect of these various conditions.

The criteria of differential diagnosis are set forth, with special reference to the "status anginosus" not infrequently met with in this condition, a picture closely simulating myocardial infarction.

Therapy of vertebro-concatenated angina is often rewarded by spectacular results if the somatic component is treated by extension of the spine, and/or procaine infiltration of the pain area. Treatment of the cardiovascular component on conventional lines, however, is mostly deceptive.

For these reasons, knowledge of the peculiar forms of angina described above is of paramount clinical importance.

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Analysis of the V_{3R} Lead As a Mass-Screening Device

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A previous publication[1] introduced the concept of utilizing a single electrocardiographic lead from the right precordium (V_{3R}) as a mass-screening device in school children for detecting certain types of congenital heart disease which are characterized by the presence of right ventricular hypertrophy. Since the original report, the V_{3R} lead has been used on over five thousand additional grade school children, and it is believed that a further report on the sensitivity, specificity, and efficiency of the V_{3R} lead in the detection of right ventricular hypertrophy (RVH) is in order.

As previously reported, there were two criteria for abnormality (indicating RVH) of the V_{3R} lead that were found practical for mass reading: (1) ratio of R wave to S wave greater than unity, and (2) ventricular activation time of 0.04 second or longer. If both criteria were present in the same tracing, the tracing was believed to be abnormal. If only one criterion was present, the tracing was reported to be borderline. All others were called "normal."

It is recognized that these criteria for RVH are arbitrary and could not be expected to detect RVH in all instances, but a number of factors made this screening test feasible and preferable. Simplicity of interpretation is the main virtue of the V_{3R} and the two criteria used. In adults, the limb leads (simpler to obtain for screening) in the presence of RVH show right axis deviation as the most common single manifestation.[4] However, right axis deviation is a normal finding in children and adolescents. Abnormal QRS voltages suggestive of RVH are not nearly so reliable or sensitive in the limb leads as in the right precordial leads.

In screening for RVH, one profitably makes use of a precordial lead which would detect abnormal anterior direction of either the initial or the terminal forces which comprise the mean QRS vector.[4] Unusual anterior direction of the initial 0.04-second QRS forces produces initial R waves in Leads V_1, V_{3R}, and/or V_{4R} which are taller than normal and 0.04 second or longer in duration.

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In addition, when the terminal 0.04-second vector at the QRS interval becomes more anteriorly directed than usual, an R′ wave becomes evident in Leads V_1, V_{3R}, and/or V_{4R}. This last statement also describes rSR′ patterns observed by Blount, Munyan and Hoffman[5] in patients with atrial septal defects who were felt to have RVH predominantly involving the outflow tract. The evidence presented for the concept of right ventricular outflow tract hypertrophy was quite credible, but the not uncommon occurrence of this type of pattern in normal children (so often as to make this undesirable as a criterion for RVH on a mass-screening basis[1]) needs to be explained in the same detailed fashion.

Among the three right precordial leads mentioned, Lead V_1 would be expected to produce the fewest, and Lead V_{4R} the most, false positive results when screening for RVH. On the other hand, Lead V_1 would probably miss the most, Lead V_{4R} the fewest, number of cases of early RVH. Lead V_{3R} was an arbitrary yet reasonable choice for use. Although use of the limb leads in conjunction with a right precordial lead would be a most specific electrocardiographic test for RVH, it was decided to use the V_{3R} lead alone because of a need to maintain simplicity in mass-screening procedures.

METHOD OF STUDY

A total of 6,858 grade school children whose V_{3R} leads have been recorded comprises the basis for this report. The subjects were obtained from three sources: (1) 4,394 of these children were among 6,311 screened in Grand Junction, Colorado, in a grade school heart disease screening program[2]; (2) 2,143 children were screened in Durango, Colorado, in a similar screening program in the same age-group and previously reported in part[1]; (3) the records of 321 consecutively seen children of the same age-group from the Denver Rheumatic Fever Diagnostic Clinic were analyzed. This last group of 321 children was a selected group which was not representative of a general population as found in the schools, but which was used in this study in an effort to include more cases of heart disease. Most of these 321 children were referred to the Diagnostic Clinic for evaluation of heart murmurs, and most had normal hearts with functional murmurs. The 321 from the Rheumatic Fever Diagnostic Clinic are comparable to the others seen in the schools in that they are from the same age-group, the same state, and were not hospitalized patients.

Tracings of Lead V_{3R} obtained in the schools were recorded by school nurses (R.N.) especially trained for the purpose. Portable electrocardiographs of various makes were used. Volunteer P.T.A. mothers assisted in dressing and undressing the children and strapping on the extremity leads. Instead of electrode paste, alcohol sponges were used to cleanse the skin and insure proper electrode contact. The V_{3R} tracings of the 321 children from the Rheumatic Fever Diagnostic Clinic were part of the complete 13-lead electrocardiograms routinely obtained on every patient at the clinic and were recorded in routine fashion by a technician at the University of Colorado Medical Center.

Every tracing from every child had been closely scrutinized at least three times. Exact measurements were taken whenever a tracing appeared to contain either criterion of abnormality. All data were recorded on I.B.M. cards and mechanically sorted so as to reduce the number of errors to a minimum.

RESULTS

Table I shows a fairly even sex distribution, but a preponderance of children in the younger ages, especially six-year-olds. This is due to the fact that the children from Durango were screened over a period of 3 school years, with the second and

third years being devoted to children not previously screened (predominantly first graders). This population age distribution may bias this analysis of the V_{3R} lead, since the normal relative right ventricular preponderance in very young children could easily cause an excess of false positive tracings in children as old as the group being studied.

TABLE I. COMPARISON OF SEX WITH AGE

SEX	AGE IN YEARS								TOTAL
	6	7	8	9	10	11	12	13 OR OLDER	
Male	657	571	540	573	527	472	155	18	3,513
Female	617	571	569	516	485	454	117	16	3,345
Total	1,274	1,142	1,109	1,089	1,012	926	272	34	6,858

The cases of congenital heart disease in Table II were divided into those with RVH and those without. This division cut across diagnostic categories, since individual differences in stage and rate of progression of disease results in different findings in various individuals with the same anatomic lesion.

TABLE II. COMPARISON OF V_{3R} INTERPRETATION WITH DIAGNOSES AS OBTAINED IN COMPLETE EXAMINATION

V_{3R} INTERPRETATION	FINAL DIAGNOSES						TOTAL
	C.H.D.		R.H.D.	OTHER H.D.	ECG ABNORMALITIES*	NORMAL	
	RVH	OTHER TYPES					
Abnormal	18	1	0	0	3	50	72
Borderline	4	10	3	1	0	507	525
Normal	4	29	31	0	2	6,195	6,261
Total	26	40	34	1	5	6,752	6,858

*Without organic heart disease.

RVH = Right ventricular hypertrophy. C.H.D. = Congenital heart disease. R.H.D. = Rheumatic heart disease. Other H.D. = Cor pulmonale secondary to prolonged severe asthma.

Table III tabulates the specific types of congenital heart disease associated with RVH and relates them to the V_{3R} interpretation. Scrutiny of Table III reveals that there was no preponderance of any one lesion in the "normal" V_{3R} category. The 3 atrial septal defects in the "borderline" V_{3R} category merely reflect the over-all preponderance of this condition in the total number of cases of RVH. Of the 4 cases of RVH with "normal" V_{3R} leads, 3 were from the records of the Rheumatic Fever Diagnostic Clinic (atrial septal defect, pulmonic stenosis, idiopathic pulmonary hypertension). The case of idiopathic pulmonary hyper-

tension was diagnosed after cardiac catheterization. The case of tetralogy of Fallot with a "normal" V_{3R} lead is classified thus with some misgivings, since there is doubt as to the technical accuracy of the tracing. It is included to avoid favorable bias, although it may, in turn, cause unfavorable bias.

To be complete, the diagnoses of congenital heart disease without RVH have also been compared with the V_{3R} lead interpretation.

The case of ventricular septal defect without RVH but with an abnormal V_{3R} was from the records of the Rheumatic Fever Diagnostic Clinic. In Table IV, as in Table III, there is a preponderance of one diagnosis, in this instance that of ventricular septal defect.

The diagnoses listed in Tables III and IV have been made with varying degrees of substantiation. Some of the diagnoses have been substantiated by surgery, some by cardiac catheterization, and others have been readily made by a comprehensive clinical examination including fluoroscopy. On the other hand, some of the diagnoses would benefit considerably if supported by a cardiac catheterization, and one or two by a repeat cardiac catheterization. Thus, there is a considerable range of certainty in some of the diagnoses, and this range is most pronounced in the cases obtained from the Rheumatic Fever Diagnostic Clinic, especially in the most critical cases as pertains to this analysis (the case of abnormal V_{3R} in a VSD without RVH and the 3 cases with RVH and a normal V_{3R}).

TABLE III. COMPARISON OF DIAGNOSES OF RVH CASES WITH V_{3R} INTERPRETATION

V_{3R} INTERPRETATION	TOTAL	DIAGNOSES				
		ASD	VSD	TETRALOGY	PULMONIC STENOSIS	IDIOPATHIC PULMONARY HYPERTENSION
Abnormal	18	13	1	1	3	0
Borderline	4	3	0	0	1	0
Normal	4	1	0	1	1	1
Total	26	17	1	2	5	1

In considering the V_{3R} lead as a mass-screening device for RVH it is necessary to consider its specificity for RVH and its sensitivity in the detection of RVH. In regard to the specificity of the V_{3R} leads for RVH, should one regard as "positive" only those cases with abnormal V_{3R} leads, and thus obtain 18 cases of RVH from a total of 72 positives? Or should one regard both the abnormal and borderline V_{3R} leads as "positive" and obtain 22 cases of RVH from a total of 597 positives? When one considers the large number of false positives in the borderline V_{3R} group, it is difficult to screen at other than the abnormal V_{3R} level. This results in a specificity value of 18/72 or .250. This, in turn, affects the sensitivity of the test in that 18 of the 26 cases of RVH would have been discovered, yielding a sensitivity value of 18/26 or .692.

TABLE IV. COMPARISON OF DIAGNOSES OF CONGENITAL HEART DISEASE WITHOUT RVH WITH V_3R INTERPRETATION

V_3R INTERPRETATION	TOTAL	DIAGNOSES										
		ASD	VSD	PULMONIC STENOSIS	AORTIC STENOSIS	COARCTATION	PDA	UNCLASSIFIED	A-V COMMUNIS	MITRAL INSUFFICIENCY (C.H.D.)	MARFAN'S SYNDROME	DEXTROCARDIA
Abnormal	1	0	1	0	0	0	0	0	0	0	0	0
Borderline	10	1	5	1	2	0	1	0	0	0	0	0
Normal	29	1	8	1	4	4	3	4	1	1	1	1
Total	40	2	14	2	6	4	4	4	1	1	1	1

If it were decided to screen out "positives" at the borderline V_{3R} level, the specificity of the test would be lowered to 22/597 or .037, and the sensitivity of the test would be raised to 22/26 or .846. To compare these two screening levels an "index of efficiency" may be computed which is the product of the specificity and the sensitivity values. This is presented in Table V. Thus, the efficiency of the screening method is vastly increased by limiting the "positives" to the abnormal V_{3R} category. However, almost one third of the cases of RVH would be missed, if these figures are reliable.

TABLE V. COMPARISON OF SCREENING LEVELS WITH SPECIFICITY, SENSITIVITY, EFFICIENCY

POSITIVE V_{3R} INTERPRETATION	SPECIFICITY	SENSITIVITY	INDEX OF EFFICIENCY
Abnormal only	.250	.692	.173
Abnormal and Borderline	.037	.846	.031

DISCUSSION

As was previously mentioned, the certainty of diagnosis in each case was not always so great as could be desired. Since some of the most doubtful cases were also some of the most critical cases, the reliability of the findings must be further qualified.

Let us assume a fair degree of reliability of the figures herein presented, indicating that the V_{3R} lead is not an exceptionally efficient method of screening for RVH, as the figures appear to show. Another and perhaps more significant objection to the use of the V_{3R} lead alone as a mass-screening device for detecting heart disease in children is the fact that it focuses on too narrow a segment of the total organic heart disease encountered in the population being screened. Rheumatic heart disease and congenital lesions causing left ventricular or combined ventricular hypertrophy are not screened out by the V_{3R} lead. Perhaps this screening test could be improved by adding a left precordial lead or even by using the three standard limb leads instead of precordial leads. Indeed, the use of a complete 13-lead electrocardiogram might not be an impractical screening device in the proper hands.

It is believed that further work should be devoted to improving methods for using the electrocardiograph as a screening device for heart disease, since it has a number of advantages for this purpose: (1) It is readily portable and may be used almost anywhere. (2) It is relatively simple to operate. (3) A minimum of highly trained personnel is required for operation. (4) Operating expenses are low.

It might be pointed out that a mass-screening method such as the physical examination might be considerably enhanced if the V_{3R} lead, with or without other leads, were to be used as an auxiliary method in conjunction with the physical examination. This phenomenon has been noted when the V_{3R} lead tracing is obtained just prior to the physical examination and is attached to the child's record card.[3]

SUMMARY

Three groups of children screened for heart disease and subjected to a recording of the V_{3R} lead were combined and analyzed with respect to the sensitivity and specificity of detection of RVH by the V_{3R} lead. The results seem to indicate that the V_{3R} is not very efficient when used alone as a mass-screening method for detection of RVH in grade school children. However, the usefulness of the V_{3R} lead when used with other ECG leads or other examining procedures is still great.

I wish to express my gratitude for the invaluable editorial comments of Dr. H. J. Dodge and Dr. M. S. Hoffman.

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Experimental and Laboratory Reports

Pharmacologic Observations on a More Potent Benzothiadiazine Diuretic (Be. 724-A*)

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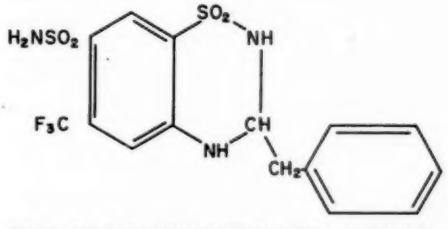
INTRODUCTION

The newest analogue (Be. 724-A) in the benzothiadiazine family of potent oral diuretics represents another advance in the continuing search for the "ideal diuretic." This continued search for more satisfactory diuretics has as its goal, primarily, a decrease in kaluretic activity and other associated metabolic disturbances, and, secondarily, an increase in potency.

The structural formula of this new drug (Fig. 1) differs from that of dihydroflumethiazide in the addition of a benzyl group to the heterocyclic ring.



3-benzyl-3,4-dihydro-6-(trifluoromethyl)
2H-1,2,4-benzothiadiazine-7-Sulfonamide,
1,1-dioxide

Fig. 1.—Structural formula of Be. 724-A.

MATERIALS AND METHODS

A. *Dose Response Curve.*—Using techniques previously described for the bioassay of diuretics,[1] we conducted a pilot study to determine the dose response curve of Be. 724-A, the experimental diuretic. Briefly, 10 patients with hypertensive cardiovascular disease were maintained under controlled metabolic conditions. At the time of study all were free of detectable edema. They were given a diet which contained 50 mEq. of sodium, and they drank 3,000 ml. of distilled water

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per day. Daily weights were obtained prior to breakfast, after voiding. Twenty-four-hour urines were collected and analyzed for sodium and volume. The drug was given in progressively incremental doses, beginning with 1.25 mg. and extending to 10 mg. as a single dose. Each of the doses was given once to 5 different patients.

B. *Determination of Potency.*—The significant points of the dose response curve were established by the pilot study and found to be between 2.5 and 5 mg. Then the drug was administered to the 10 subjects of the study at both of these doses, and the observations previously described were made. The data were then subjected to the statistical analysis of variance for the determination of significance, and a computation of the potency estimation was made. These data were then compared to those of a standard, meralluride (Mercuhydrin), which has an arbitrary potency of one.

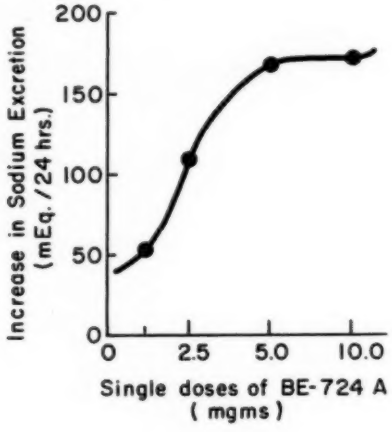

Fig. 2.—The significant part of the dose response curve for Be. 724-A lies between the 2.5 and 5.0-mg. doses.

C. *Electrolyte Excretion Effects.*—The drug was administered to 5 patients (each received doses of 2.5, 5.0, and 10.0 mg. at intervals of 5 days), and the urinary electrolyte excretion effects were studied. These studies consisted of the analysis of the urine for volume, sodium, potassium, pH, chloride, and bicarbonate in six fractional periods during the 24 hours following each dose (three consecutive 2-hour periods followed by three consecutive 6-hour periods).

D. *The Effect on Body Weight, Sodium Excretion, and Serum Biochemical Architecture.*—The drug was administered at a dose of 5.0 mg. to 5 mildly edematous patients for 5 consecutive days. The blood was analyzed for significant electrolyte changes (sodium, potassium, carbon-dioxide combining power, chloride, urea nitrogen, and hematocrit), and the urine was analyzed for sodium and volume. Body weight was determined daily. This study was made in order to determine the repetitive effectiveness of the drug as well as to observe any development of tolerance. It was also used to observe the effects on serum biochemical architecture.

E. *Therapy in Various Edematous States.*—The drug was given to patients with edema (mild to moderate) of varied etiology in a dose of 5 mg. daily for 21 days, and observations on body weight, serum electrolytes (sodium, potassium, chloride, carbon-dioxide combining power), blood urea nitrogen, and hematocrit were made in the control state and at the end of 7 and 21 days. There were 8 patients with cardiac edema, 2 with cirrhotic edema, 4 with nephrotic edema, 2 with edema induced by steroid therapy, and 4 women in the third trimester of pregnancy.

F. *Effect in Antihypertensive Therapy.*—Five patients in each of four groups were given the drug in a dose of 10 mg. daily for 3 weeks. The first group consisted of patients with hypertension who had been observed for 3 consecutive weeks prior to therapy. The second group consisted of patients who were receiving rauwolfia (Raudixin, 100 mg. daily, b.i.d.) for a period in excess of 3 months. The third group consisted of patients who had been receiving rauwolfia in addition to mecamylamine (in ganglionic blocking doses), but who were less than optimumly controlled for a period in excess of 3 months. The fourth group consisted of patients who had been fairly

well controlled on a regimen consisting of rauwolfia, mecamylamine, and chlorothiazide (500 mg. daily). In this group the drug was substituted for the previous chlorothiazide therapy in a dose of 10 mg. Observations were then made at the end of the first and third week.

RESULTS

A. *Dose Response Curve.*—The pilot study revealed that the significant part of the dose response curve was between the 2.5 and 5.0 mg. dose. The 10.0 mg. dose was not associated with any evidences of clinical toxicity. However, at a dose of 10 mg. the sodium response did not increase significantly beyond that observed with the 5.0-mg. dose (Fig. 2), indicating that administration of doses greater than 5 mg. per day will usually serve no therapeutic use unless a problem such as faulty gastrointestinal absorption is encountered.

B. *Determination of Potency.*—Ten observations made on the two doses of 2.5 and 5.0 mg. revealed a significant increase in the urinary volume and sodium and a decrease in weight (Table I). The average increase in urinary sodium was 110 mEq. per 24 hours over control at the 2.5-mg. dose, and an average increase of 170 mEq. per 24 hours over control at the 5.0-mg. dose. These changes were paralleled by changes in urinary volume and loss of weight.

TABLE I. DIURETIC RESPONSES TO SINGLE DOSES OF BE. 724-A
(AVERAGES OF DETERMINATIONS ON 10 PATIENTS)

	2.5 MG.				5.0 MG.			
	C	D	I	P VALUE*	C	D	I	P VALUE*
Urine Volume (L./24 hr.)	3.1	3.8	.7	.01	3.0	4.5	1.5	.01
Urine Sodium (mEq./24 hr.)	45	155	110	.001	46	216	170	.001
Urine Potassium (mEq./24 hr.)	25	45	20	.01	25	46	21	.01
Body Weight (Kg.)	67	66.4	−0.6	.01	66.8	65.4	−1.4	.01

*P Value: Derived from Student's "t" test.
C: Control. D: Drug. I: Increase.

After the data had been subjected to an analysis of variance, it was found that the dose response curves for Be. 724-A and meralluride are parallel and linear, and that the statistical error is not significant (Fig. 3). By direct reading of the curve it is seen that a dose of 2.5 mg. of Be. 724-A orally administered is equivalent in natriuretic potency to 1.9 c.c. of meralluride (Mercuhydrin) administered intramuscularly. Expressed in a different fashion, 2 c.c. of meralluride is equivalent to 2.8 mg. of Be. 724-A. The data revealed that the potency estimation of Be. 724-A is 1.8, whereas that for meralluride is 1.0. In other words, Be. 724-A is 1.8 times as potent as meralluride at the two doses observed.

C. *Electrolyte Excretion Effects* (*Fig. 4*).—A typical electrolyte excretion pattern at the 5.0-mg. dosage level of the drug revealed that there is a slight

increase in the excretion of potassium and bicarbonate (and pH), but these changes are not so great as those seen with chlorothiazide.[1] Aside from the fact that a greater excretion of sodium and chloride was observed at a dose of 5.0 mg., the electrolyte excretion patterns at the two doses (2.5 and 5.0 mg.) were essentially the same (Fig. 5).

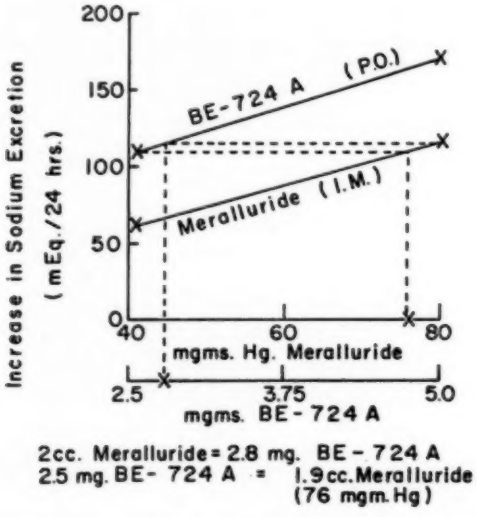

Fig. 3.—Dose response curves for meralluride and Be. 724-A for determination of comparative potency. When compared to the standard meralluride (Mercuhydrin), which has a potency estimation of one, Be. 724-A is found to be 1.8 times as potent as meralluride at the two dosage levels observed.

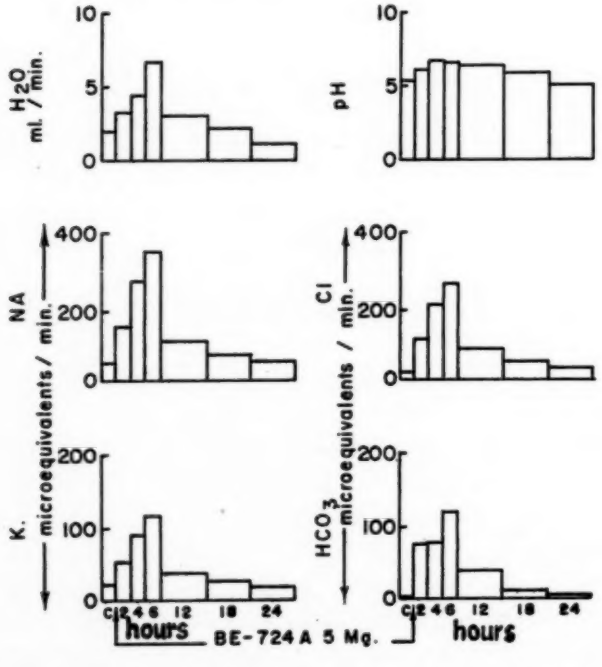

Fig. 4.—A typical electrolyte excretion pattern at the 5.0-mg. dosage level of the drug demonstrates that there is a slight increase in the excretion of potassium and bicarbonate, but these changes are not so great as those seen with chlorothiazide.

D. *The Effect on Body Weight, Sodium Excretion, and Serum Biochemical Architecture.*—There was a continuing excretion of sodium and a decline in body weight following daily therapy. No significant changes in blood urea nitrogen or hematocrit were observed. Changes in serum sodium, potassium, carbon-dioxide combining power, and chloride were not significant (Fig. 6).

E. *Therapy in Various Edematous States.*—Table II demonstrates the effectiveness of this compound as a diuretic agent in edematous states of varied etiology. Significant loss of weight was observed in all five groups, as well as slight changes in serum biochemical architecture. However, none of these changes was reflected in a change in the clinical status of the patient, except for the relief of edema.

F. *Observations on the Effectiveness in Antihypertensive Therapy.*—When this drug was used alone as the therapeutic agent in the treatment of mild hypertension, there was a significant decrease in blood pressure at the end of 3 weeks (Table III). When added to the previous antihypertensive regimen of rauwolfia alone, or rauwolfia in combination with mecamylamine, there was an additional decline in blood pressure. When chlorothiazide was replaced by this drug in the adjunctive management of severe hypertension which was being treated with rauwolfia plus ganglionic blocking agents (mecamylamine), there was no significant difference between the two compounds.

DISCUSSION

Although the recent introduction of a wide variety of potent oral diuretics has added greatly to the therapeutic tools available to the physician for edematous

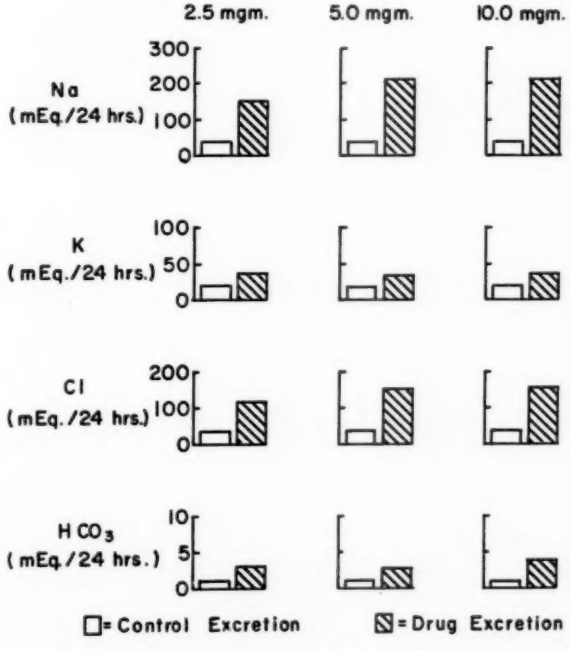

Fig. 5.—Comparative electrolyte excretion at various dosage levels of Be 724-A.

and hypertensive states, the search for the ideal diuretic—one which causes an augmentation in the output of urine, the composition of which is nearly physiological—continues.

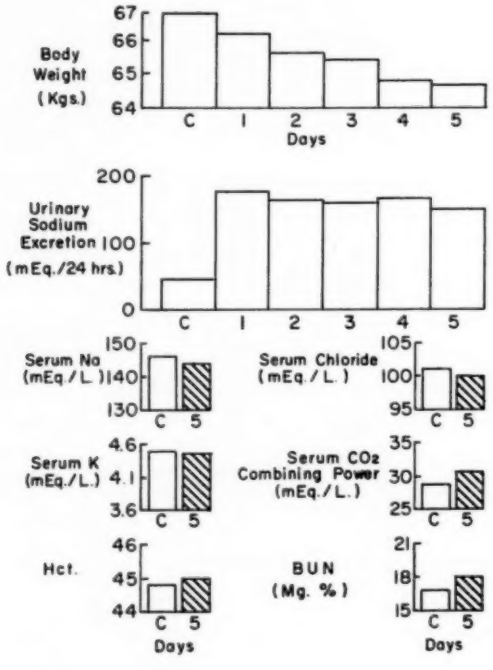

Fig. 6.—Illustration of the repetitive effectiveness of Be. 724-A, and its influence on serum biochemical architecture, in a 5-mg. daily dose to 5 patients with mild to moderate edema.

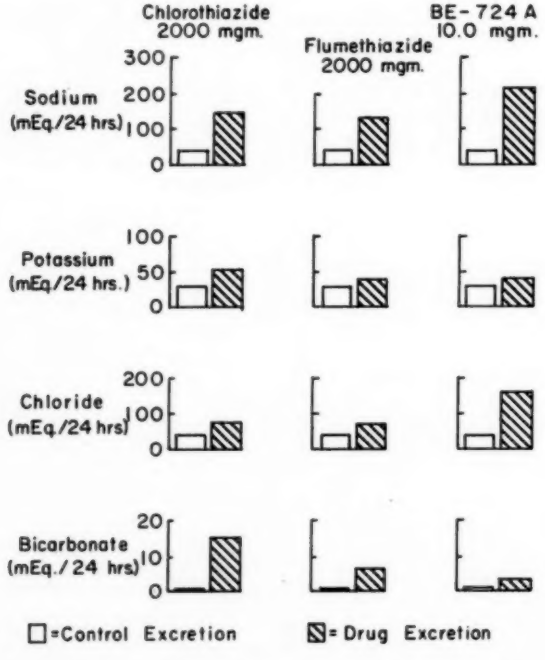

Fig. 7.—Comparative electrolyte excretion effects of various thiazide diuretics.

TABLE II. CLINICAL RESPONSES TO BE. 724-A (DOSE OF 5 MG. DAILY) IN VARIOUS EDEMATOUS STATES (AVERAGE VALUES FOR EACH GROUP)

TYPE OF EDEMA	NUMBER OF PATIENTS	PERIOD	CUMULATIVE LOSS OF WEIGHT (LB.)	SERUM ELECTROLYTES (MEQ./L.)				BLOOD UREA NITROGEN (MG. %)	HEMATOCRIT (%)
				Na	K	CO_2 CONTENT	cl		
Cardiac	8	Control		143	4.4	30	108	23	47
		Day 7	4	142	4.3	31	107	24	47
		Day 21	11	142	4.3	33	105	26	49
Cirrhotic	2	Control		132	3.3	28	90	12	42
		Day 7	7	129	3.1	28	86	13	43
		Day 21	16	127	3.1	29	85	14	45
Nephrotic	4	Control		129	4.0	24	96	34	40
		Day 7	5	126	3.9	25	94	32	42
		Day 21	13	125	3.8	27	90	31	43
"Steroid"	2	Control		145	3.6	32	93	13	40
		Day 7	3	143	3.4	35	92	15	41
		Day 21	6	143	3.4	36	89	16	41
Pregnancy	4	Control		140	4.2	30	106	11	39
		Day 7	1	140	4.2	31	103	11	40
		Day 21	5	138	4.0	34	102	12	41

TABLE III. EFFECT OF BE. 724-A AS AN ANTIHYPERTENSIVE AGENT (AVERAGE VALUES FOR 5 PATIENTS IN EACH GROUP)

ANTIHYPERTENSIVE REGIMEN IN THE "CONTROL" STATE	BLOOD PRESSURE*										
				DRUG†							
	CONTROL			ONE WEEK				THREE WEEKS			
	S	D	MBP	S	D	MBP	"P"	S	D	MBP	"P"
None	210	114	146	182	100	127	.05	158	98	118	.001
R	172	108	129	150	96	114	.05	138	90	106	.001
R + GB	148	106	120	132	88	103	.05	126	80	95	.001
R + GB + C	144	100	115	142	96	111	N.S.	140	96	111	N.S.

*Blood pressure values are recorded in the upright position.
†Drug values after addition of Be. 724-A, 10 mg. daily.
S: Systolic. D: Diastolic. MBP: Mean blood pressure (diastolic plus 1/3 the pulse pressure).
"P": P values determined by Student's "t" test.
R: Rauwolfia alone (Raudixin, 100 mg. twice daily).
R + GB: Rauwolfia plus mecamylamine in ganglionic blocking doses.
R + GB + C: Rauwolfia plus mecamylamine and chlorothiazide (500 mg. daily). Be. 724-A replacement for chlorothiazide in a dose of 10 mg. daily.

The currently available orally effective diuretics (as listed in Table IV) approach this ideal, except that they cause an excessive loss of potassium and bicarbonate. When the urinary electrolyte excretion patterns of the maximum effective dose of chlorothiazide,[1] flumethiazide,[2] and Be. 724-A are compared (Fig. 7), Be. 724-A shows a significantly greater increase in natriuresis ($p < .01$) and less of an increase in kaluresis ($p < .05$) and bicarbonate ($p < .01$) excretion. Although this decreased output of bicarbonate anion and increased loss of chloride might increase the tendency toward hypochloremic alkalosis, the conservation of potassium (Table I) is important, both objectively and subjectively. The patients report that they feel much better, and they do not complain of weakness and fatigue. Earlier experimental[3,4] and clinical[5] reports indicated that hypokalemia and potassium-deficient states resulted in a decrease in blood pressure, or hypotension, but a recent report[6] indicates that potassium may have a protective action against the pressor action of increased sodium loads, or increased sodium/potassium ratios.

TABLE IV. COMPARISON OF POTENCY OF VARIOUS DIURETIC AGENTS

DRUG	ROUTE OF ADMINISTRATION	POTENCY ESTIMATION*
Be. 724-A	Oral	1.8
Hydrochlorothiazide (Hydrodiuril)	Oral	1.4
Hydroflumethiazide (Diademil)	Oral	1.3
Meralluride (Mercuhydrin)	I.M.	1.0
Chlorothiazide (Diuril)	Oral	0.8
Flumethiazide (Ademol)	Oral	0.7
Mercaptomerin (Thiomerin)	I.M.	0.5
Chlormerodrin (Neohydrin)	Oral	0.5
Acetazoleamide (Diamox)	Oral	0.25

*Determined from previous analysis of variance of these drugs.

Be. 724-A appears to act in the same manner as do the prior members of this heterocyclic group. It is the most potent diuretic on a weight basis (Fig. 2), maintains its potency with chronic administration (Fig. 6), and is effective in various edematous and hypertensive states (Tables II and III).

The drug has a high therapeutic index, and continued use causes no significant alterations in serum electrolyte values (Fig. 6). This is especially valuable in view of its potency. Using intramuscularly given meralluride as a standard of "one," the potency of various available diuretics is compared in Table IV.

Recent criticisms of this type of diuretic bioassay and potency estimation have been advanced.[7] These criticisms may have merit, but data to dogmatically affirm such criticisms are neither presented nor at hand. At this point we would like to re-emphasize the basis of present-day statistically oriented diuretic bioassay techniques, which have strictly controlled metabolic conditions. Reports of such studies are true for the conditions of those studies but may not be directly transferable to a large outpatient or clinical basis. Individual variations in such factors as gastrointestinal absorption, amount of edema, degree of cardiac de-

compensation, diet, medication and response to it—the total clinical picture of the patient—may somewhat alter the individual response, especially when a comparison is made with the response to intramuscular meralluride, which is completely absorbed. However, such studies are indispensable as a guide to clinical potency, efficacy, and value prior to general use, which generally entails less frequent and less controlled observations.

SUMMARY

3-Benzyl-3, 4-dihydro-6-(trifluoromethyl) 2H-1,2,4-benzathiadiazine-7-sulfonamide, 1,1-dioxide is an effective oral diuretic, with 2.8 mg. of the drug being equivalent to 2 c.c. of meralluride intramuscularly.

When compared to other members of this heterocyclic group of compounds, the drug shows a significantly increased natriuresis and decreased loss of potassium and bicarbonate. In this respect it more closely approaches a natural or "ideal diuretic."

It is effective upon continuous administration, and causes no significant serum biochemical changes.

It is effective in a wide variety of edematous and hypertensive states and represents a (significant) advance in diuretic therapy.

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Activation of the Interventricular Septal Myocardium Studied During Cardiopulmonary Bypass

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The normal sequence of activation of the interventricular septum of the canine heart has been studied by several groups of investigators. Lewis and Rothschild[1] presented the first comprehensive report on septal activation, and in a later publication, Lewis[2] concluded that the first area to be depolarized in the canine heart during normal atrioventricular propagation was high on the left side of the septum, and that activity then spread to the apex and base of the left septal surface. He also noted that the activation times varied in the middle of the left septal surface. The earliest depolarization of the right ventricular septal surface was found to occur near the base of the anterior papillary muscle. Excitation of the right mid-septum followed this initial invasion, and activation was latest in the vicinity of the septal leaflet of the tricuspid valve. Subsequently, Sodi-Pallares[3] measured septal activity with plunge electrodes inserted through the ventricular wall into several points on the septum. He concluded that mean septal excitation occurred from apex to base. A similar conclusion was reported by Burchell,[4] on the basis of changes in vectorcardiographic records before and after dissections of the heart. Scher[5,6] recently utilized an improved technique of repeated insertions of multipolar plunge electrodes and reached conclusions in general agreement with those of Lewis. However, the site of earliest intraventricular activity was located halfway between the apex and base on the left septal surface rather than high on the septum.

Numerous small differences are apparent among all of these previous reports. Also, studies of septal activation after production of right or left bundle branch block have given inconsistent results.[3,7] Many of these discrepancies may reflect the varying experimental techniques employed. Tracings of septal activity were recorded only infrequently from both the earliest and latest areas of septal depolarization in any given animal. Predetermined, accurate placement

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in the septum of the plunge electrodes inserted through the ventricular wall is difficult because of variations in the surface configuration of this structure. Also, techniques of placing plunge electrodes are often, if not always, associated with local injury of tissue and focal conduction block. In fact, the production of bundle branch block has been clearly demonstrated when a plunge electrode enters the bundle tissue.[5]

Recently, a technique has been developed[8] which avoids these technical problems. Records are obtained from open chambers of the in situ beating canine heart under direct vision while the dog is on cardiopulmonary bypass. Both surfaces of the interventricular septum can be investigated by manual placement of a roving electrode on as many selected points of the endocardial surface as desired. This technique has been employed to measure the sequence of activation of both septal surfaces during normal atrioventricular excitation and following right or left bundle branch block.

METHOD

A. *Perfusion Preparation.*—Mongrel dogs weighing 18 to 24 kilograms were anesthetized with intravenous sodium Pentothal and placed on controlled respiration. The chest was opened transsternally through the fifth intercostal space. Tapes were placed around the superior and inferior venae cavae, and the pericardium was opened widely. Heparin, 250 U.S.P. units per kilogram, was given intravenously before introducing catheters through the azygos vein into the superior vena cava and directly into the inferior vena cava. The systemic venous blood was drained by gravity into a rotating screen-oxygenator[9] primed with fresh canine blood containing 400 U.S.P. units of heparin per 100 c.c. After oxygenation, the blood was recirculated to the animal through a cannula inserted in the femoral artery. The dog was placed on total pump-oxygenator perfusion by tightening the tapes about the cavae. The right atrium and the right and left ventricles were then opened. Coronary artery perfusion was present throughout the procedure.

B. *Bundle Branch Block Preparation.*—The surgical technique of producing bundle branch block was aided by studying the anatomic distribution of the septal Purkinje fiber network. Tincture of iodine, 4 per cent, was applied to postmortem canine heart specimens in order to stain the glycogen-containing Purkinje fibers. When this method is used, the right main bundle branch is first seen on the right ventricular septal surface beneath the anterior third of the septal leaflet of the tricuspid valve. This bundle courses posteriorly to the base of the superior papillary muscle and then toward the apex of the heart. As the main bundle approaches the base of the anterior papillary muscle, a branch is distributed superiorly to the anterior septal surface. The main bundle usually continues onto the base of the anterior papillary muscle, where it frequently divides into two branches. One division travels as a free-running band to the right ventricular wall, whereas the other division continues toward the inferior papillary muscle and posterior portion of the septal surface. The left bundle branch appears on the left septal surface below the junction of the right coronary and noncoronary aortic cusps. A myriad of fibers are distributed from this region to the entire left septal surface; two larger bands, "the false tendons," course toward the anterior and posterior papillary muscles on the ventricular wall.

Complete bundle branch block was produced by an incision near the origin of the right or left bundle branch. The right bundle branch was interrupted by an incision 1.5 mm. in depth and extending 1 to 2 cm. posterior to the base of the superior papillary muscle. The left bundle branch was interrupted beneath the aortic valve with a curved incision that extended from below the mid-portion of the base of the right coronary aortic cusp to the mid-portion of the base of the noncoronary aortic cusp.

C. *Recording Techniques.*—Small, lightweight plastic plaques, measuring approximately 0.5 cm. by 1 cm., were sutured to the lateral epicardial surface of both ventricles, well removed from the cardiotomy incisions. Two fine silver wire contacts, 1 mm. apart, were embedded in these

plastic plaques in order to record unipolar or bipolar electrograms from each ventricle. Shortly after the electrodes were attached, sharp deflections were consistently recorded from the underlying muscle. These tracings, as well as standard limb electrocardiograms, served as time references for all measurements of septal activation. In studies involving either a right or left bundle branch block the electrogram of the unaffected ventricle was used as the time reference. In some experiments a bipolar electrogram recorded from the bundle of His was employed as an additional time reference. Electrical activity of the septal endocardium was recorded through two fine silver wire contacts, 0.5 mm. apart, located in the tip of a curved plastic probe. This probe was held lightly under direct vision on selected points of the septal surface (Fig. 1). The tricuspid and pulmonary valves and the superior, anterior, and posterior papillary muscles served to orient the position of the exploring electrode on the right septal surface (Fig. 2,*A*). On the left surface the aortic and mitral valves, the anterior and posterior papillary muscles, and the point of emergence of the left bundle branch determined the position of the exploring electrode (Fig. 2,*B*).

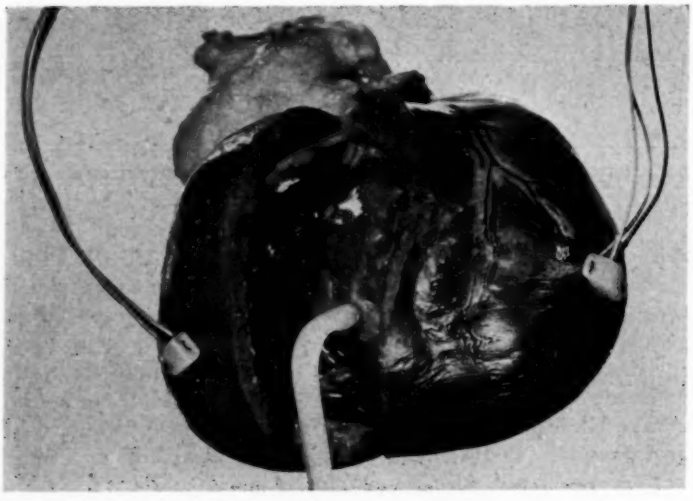


Fig. 1.—Demonstrates reference electrodes sutured to the right and left ventricular epicardium and a roving electrode positioned at a point on the right septal surface.

Electrograms were recorded from multiple points, first on the right and then on the left septal surface. The temperature of both septal surfaces was then measured and electrograms were again recorded from the septal points previously studied. After the temperature measurements were repeated, either a right or a left bundle branch block was produced. Changes in the standard limb leads and delay in time of activation of the surface electrode of the involved ventricle verified the existence of bundle branch block. Bipolar electrograms and temperatures were then recorded from the same points as prior to the bundle branch block. Three or more complexes were recorded at each location on the septum. If the septal electrographic complex was monophasic, the peak of the sharp deflection was selected for time measurements. If the wave was diphasic, measurement was made from the instant the trace crossed the line of zero potential. Local septal depolarization was timed with respect to activity at the site of the appropriate epicardial reference electrode by measuring three or more complexes and expressing the average time difference, in milliseconds, as plus (after) or minus (before) values with respect to the time of epicardial activity.

All records were monitored on an Electronics for Medicine 8-channel switched-beam oscilloscope and photographed on paper moving at speeds of 100 or 200 mm. per second. Bipolar electrograms were used to time septal activity and the activity of the epicardial surface of both ventricles. Ventricular extrasystoles or alterations of the configuration of the complex recorded through the exploring electrodes indicated that local irritation had occurred. In such instances a decrease in the contact pressure or readjustment of the exploring electrode was sufficient to

restore normal activity. Rectal temperature was monitored throughout the experiment by means of an indwelling thermistor. Body temperature was maintained above 90°F. by the application of external heat to the oxygenator and dog. The temperatures of the right and the left interventricular septal surfaces, as well as of the epicardial surfaces, were recorded intermittently by means of a miniature, glass-enclosed thermistor and sensitive galvanometer. Cardiac temperatures

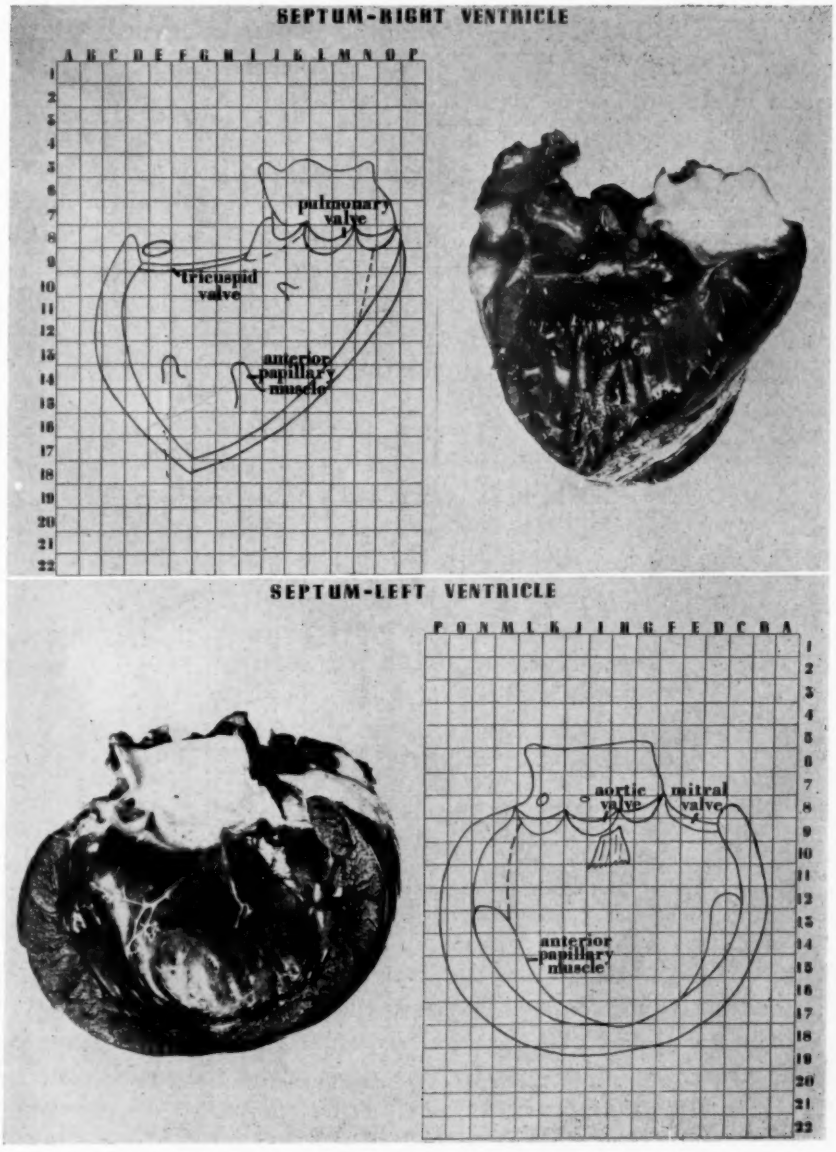


Fig. 2.—Right (*A*) and left (*B*) septal surfaces with corresponding blocked diagrams used in charting conduction.

varied from 88.2 to 92.3°F. in different experiments. Arterial blood pressure was measured through a polyethylene catheter inserted into one of the femoral arteries and attached to a Statham pressure gauge. These records were transcribed onto a direct-writing Sanborn 4-channel recorder. In all studies the mean blood pressure was maintained above 100 mm. Hg by a perfusion flow of 60 to 80 c.c./Kg./min.

RESULTS

A. *Adequacy and Reproducibility of Records.*—If closely approximated bipolar electrodes are in direct contact with cardiac muscle and in proper relation to the direction of spread of excitation, the electrographic deflection is of short duration.[10] Moreover, it has been demonstrated that such a deflection is synchronous with the depolarization recorded through an intracellular microelectrode from the fibers immediately adjacent to the bipolar surface electrode.[11] In the present investigation all records of activation of the septal surface revealed sharp deflections of short duration (Figs. 3, 6-10). An additional indication that the exploring electrodes recorded from only a discrete and localized area was obtained from tracings which showed electrical activity of subendocardial Purkinje fibers as well as septal muscle (Fig. 3). Also, the large differences in the time of activation recorded from certain closely adjacent points reflect the extent to which the exploring electrode was influenced by depolarization of tissue directly beneath the tip. These observations suggest that the records obtained through the exploring electrode were adequate for timing local depolarization.

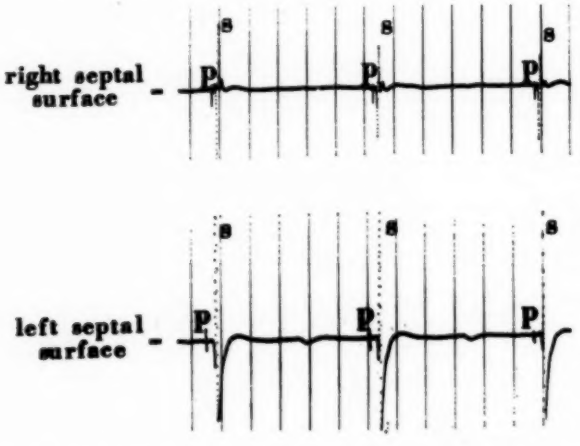


Fig. 3.—Purkinje (*P*) and septal myocardium (*S*) tracings obtained at one point on the right and left septal surfaces.

An additional consideration is the accuracy with which the exploring electrode could be positioned on points previously studied and the consistency of results obtained over an appreciable interval of time. Information relating to these questions is presented in Fig. 4. In this experiment the time of activation of 20 points on the right septal surface was determined, and then, after a study of the left septal surface, the records from the same 20 points on the right side were repeated. It can be seen that for 11 points the two sets of determinations agreed within 3 msec., and that the maximum difference for two readings from any one point was 10 msec. Changes in the alignment of the exploring electrode on the same site resulted in changes in the configuration of the electrogram and, as a result, a variation of 2 to 4 msec. in the time of the major deflection. Also, it will be noted that large differences between repeated measurements of the activation time of a single point are encountered only in locations at which closely adjacent

areas show wide differences in the time of depolarization. The consistency of the results obtained with the technique therefore appears acceptable when the degree of reproducibility of control records is considered in relation to the order of magnitude of change in activation time produced by bundle branch block.

B. *The Sequence of Activation of the Right and Left Septal Surfaces.*—The sequence of activation of the right septal surface was determined from records obtained at 16 to 45 points in different experiments. The time of depolarization at each point was determined in relation to the time of the reference electrogram and plotted as milliseconds before (−) or after activity at the reference site (Figs. 4, 6, 7, and 10). Although there is considerable individual variation, the results obtained from all experiments have several common characteristics.

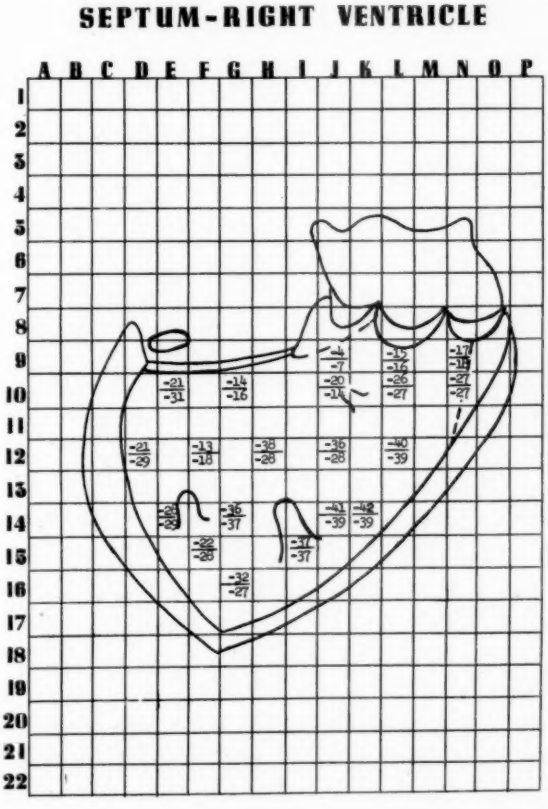


Fig. 4.—Demonstrates the consistency of records when repeated at 20 points on the right septal surface. The numbers represent the difference in milliseconds between activation of the septal points and the reference electrode. The minus sign (−) indicates that the septal point was activated earlier than the reference electrode.

In agreement with the conclusions of other investigators, the data from these experiments show that the base of the anterior papillary muscle is excited early in the normal atrioventricular sequence. However, it is apparent that the site of earliest activity is located on the surface of the septum above and anterior to this muscle. These earliest points of septal activity often demonstrated electrical activity of the subendocardial Purkinje fibers preceding the septal myocardial electrogram (see Fig. 3). In addition, in all experiments there was considerable

difference in the time of activation of adjacent septal points even in the area of the right septal surface showing earliest activity; this finding is in contrast with the results obtained from the left septal surface (see below). Finally, the spread of activity over the entire right septal surface required from 35 to 60 msec.

The plots of individual determinations give some indication of the mean direction of the spread of activity over the right side of the interventricular septum. This is seen more clearly in Fig. 5. For this illustration the total time required for activation of the septum was divided into three equal parts and plotted as areas of early, intermediate, and late activation. The two experiments shown are representative of the patterns noted; in all hearts the earliest activity occupied the same general area on the right surface, but in some experiments the septum beneath the pulmonic valves fell in the intermediate, and in others in the late, activation time division. The results from all experiments show a degree of uniformity which is surprising in view of known variations in the anatomy of the septal musculature and the distribution of the specialized conducting system. In agreement with the observations of Lewis,[2] the mean direction of the spread of activity on the right septal surface is directed upward and somewhat posteriorly.

The results obtained from studies of the left septal surface were in sharp contrast to those just described. Activation of the left surface occurred quite rapidly and, with the exception of peripheral points at the base, was completed within 10 to 15 msec. (Figs. 8 and 9). The earliest activity was always recorded from the central part of the left septal surface, either just above or just below the middle; in this area, moreover, records of the activity of subendocardial Purkinje fibers were seen most frequently. Subsequent to depolarization of the central area of the septum, activity spread to the apex and base, and in the latter area, just beneath the valves, activation was most delayed. In contrast with the results of most previous studies, it was found that the earliest activity recorded from a single point on both the right and left surfaces of the septum was almost simultaneous; the greatest difference observed in any experiment was 1 to 2 msec. However, because of the almost simultaneous activation on the left, a major part of the left surface was excited prior to involvement of a comparable area on the right side.

C. *The Effect of Bundle Branch Block on Septal Activation.*—In studies of the effect of right or left bundle branch block on the sequence of septal activation, electrograms were recorded from a series of points on both surfaces, and, after division of the desired main bundle branch, records were again obtained from the same set of points. The presence of block was determined from changes in the limb lead electrocardiogram and from delayed activation at the site of the reference electrodes on the epicardial surface of the affected ventricle. Areas of the septal surface which demonstrated an appreciable delay in activation after division of a main bundle branch were thought to depend on that part of the specialized conducting system for normal activation. Areas which showed no delay after production of bundle branch block were assumed to depend on the other main bundle branch. Since anatomic studies were not made, the possible role of a medial septal branch of the specialized conducting system could not be evaluated.

In all experiments, division of the main right bundle branch caused a marked delay in activation of the anterior and middle parts of the right septal surface (Figs. 6 and 7). However, the activation time of the posterior part of the right septal surface did not always show comparable changes. In some experiments (Fig. 6) the posterior and superior margins of the right surface revealed little or no significant delay after division of the right bundle branch; in others (Fig. 7), a more or less uniform delay was apparent over the entire right side of the septum. The sequence of activation of the right surface also varied after right bundle branch block: in some animals, activity seemed to spread anteriorly from the posterior margin of the septum (Fig. 6), whereas in others, after bundle branch block, activity appeared almost simultaneously at points which normally were either early or late in the sequence of activation (Fig. 7). The magnitude of the delay in activation of points on the right septal surface after right bundle branch block varied from 9 to 62 msec., with an average of 32 msec.; the pattern of activation is the subject of future study. Activation of the left septal surface was unchanged by complete right bundle branch block (Fig. 8).

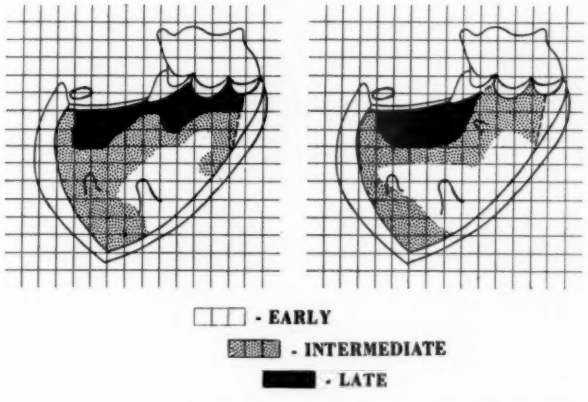
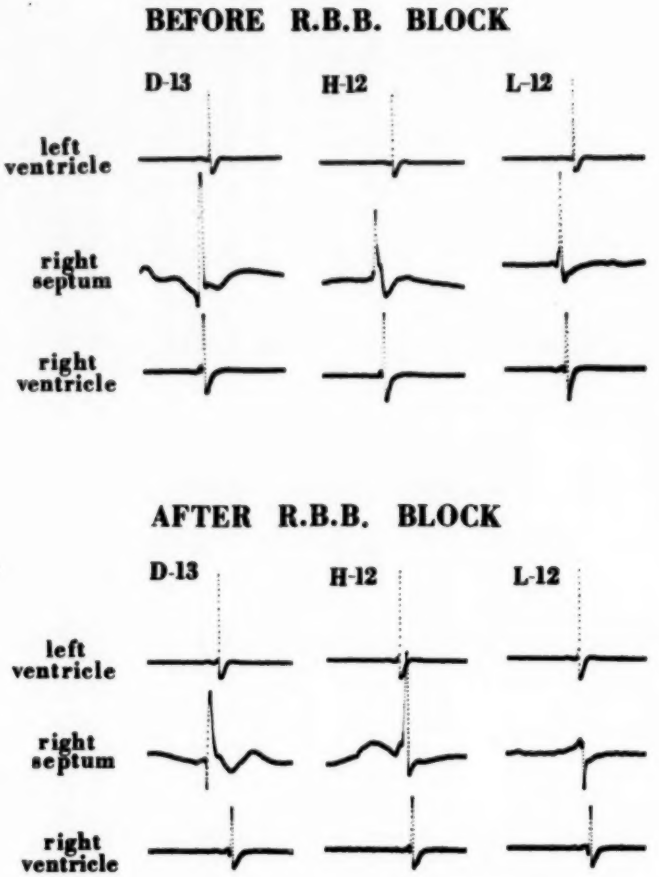


Fig. 5.—The activation pattern of the right interventricular septal surface in the canine heart in two experiments.

Because of the varied effect of right bundle branch block on the activation of the posterior part of the right septal surface, and because most studies of this surface were carried out through a right ventriculotomy which transected the greater part of the free wall of the right ventricle, several experiments were performed in order to determine the effect of dividing the free-running bundles of the specialized conducting system which extend from the base of the anterior papillary muscle to the muscle of the free wall. Division of these bundles of specialized fibers caused changes in the time of activation of only the posterior aspect of the right septal surface. The magnitude of the changes varied from minimal to delays amounting to 10 to 15 msec. These findings demonstrate that, in some hearts at least, the most posterior part of the right septal surface is normally activated by spread from the free wall of the ventricle. Unless adequate precautions are taken to avoid destruction of the conducting fibers running to the free wall of the ventricle, the posterior part of the right septal surface will show delayed activation under normal conditions, and after division of the right bundle



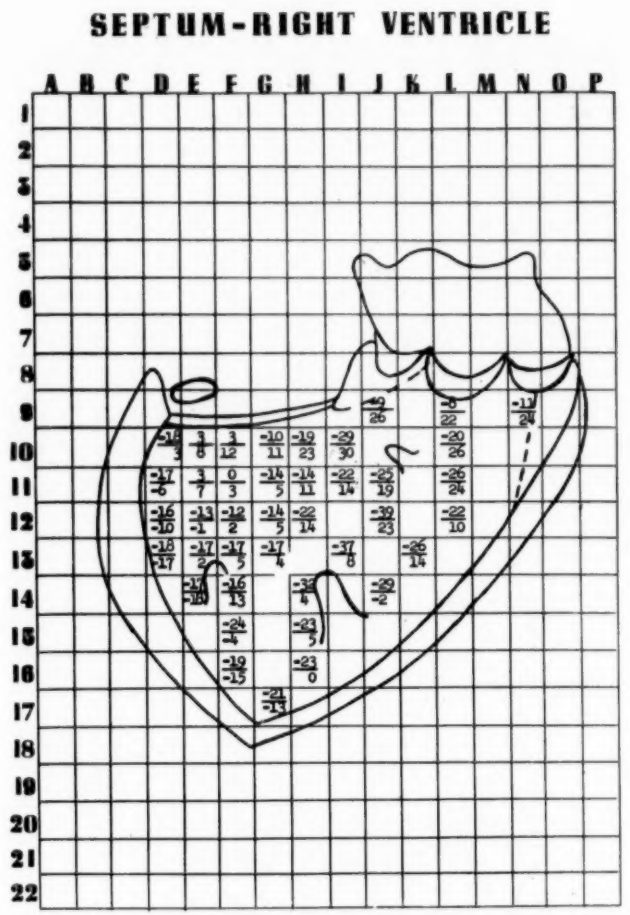


Fig. 6.—Activation of the right ventricular septal surface before and after RBBB (Example I). Numbers at each point represent the difference in milliseconds between activation of that septal point and the left ventricular reference electrode. The numbers above the line were obtained before RBBB, and those below the line after RBBB. In this and subsequent Figs. 7-10, a number preceded by a minus sign (−) indicates that the septal point was activated earlier than the reference electrode. Numbers not preceded by a minus sign were activated later than the reference electrode. A zero (0) indicates simultaneous activation of that point and the reference electrode. Note the marked delay after RBBB, except on some posterior points.

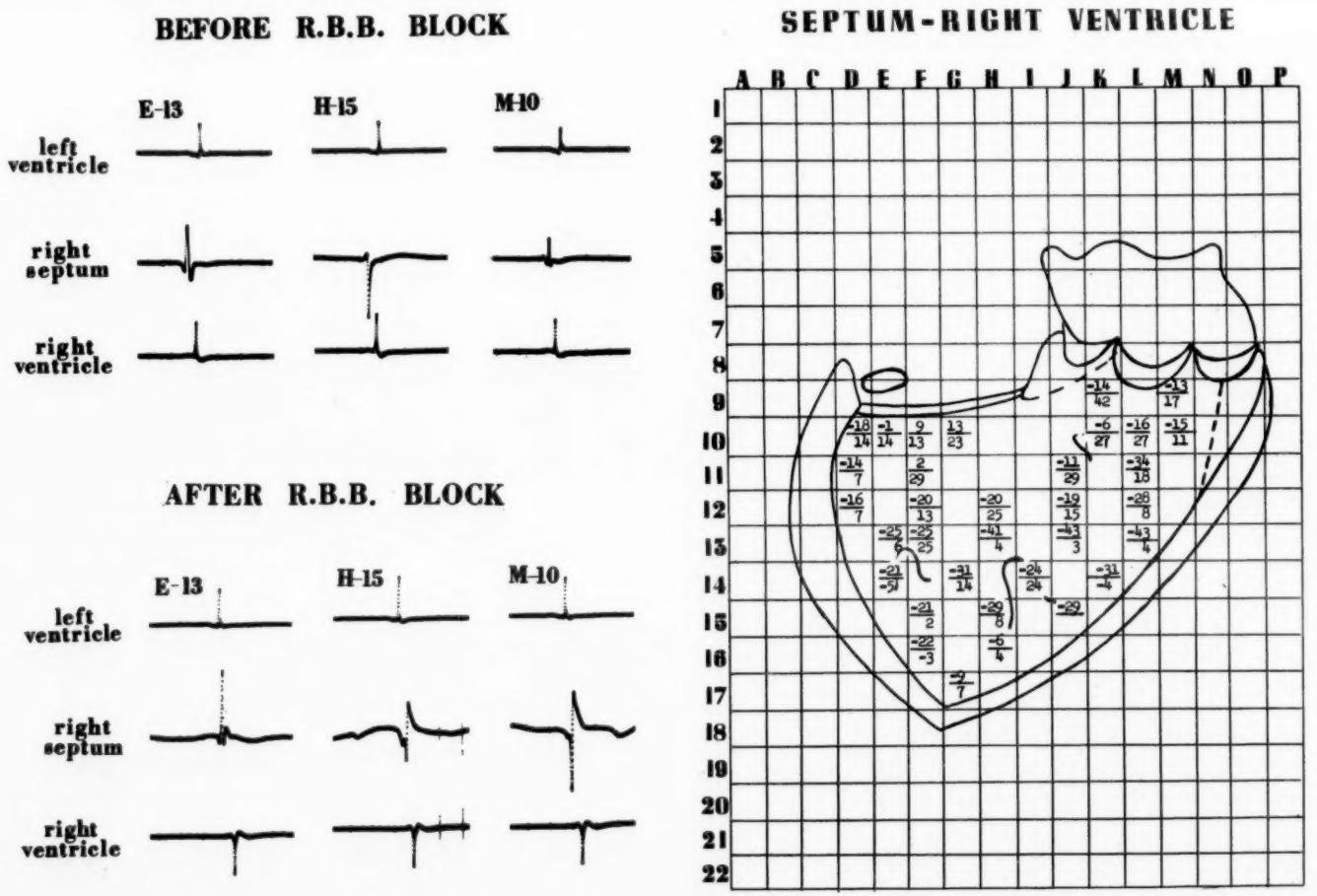


Fig. 7.—Activation of the right ventricular septal surface before and after RBBB (Example II). Reference tracings are from the left ventricle as in Fig. 6. Note delay on entire right septal surface after RBBB.

branch this same area will not necessarily show additional delay. The results described above (Figs. 6 and 7) were unchanged in experiments in which the above precautions were observed.

After division of the left main bundle branch, activation of the entire left septal surface was delayed (Fig. 9). As on the right side, the magnitude of the delay at different points varied; the minimum was 15 and the maximum was 68 msec., with an average of 35 msec. The pattern of activation of the left surface after left bundle branch block showed considerable variation in different animals and is the subject of further study. Division of the left bundle branch was without effect on the sequence of activation of the right septal surface except in one experiment. In this animal, two points on the posterior part of the right surface were delayed 3 and 7 msec. by left bundle branch block.

DISCUSSION

A technique recently described by this laboratory[8] for the study of conduction in the in situ beating heart has been used to map the sequence of activation of the septal surfaces of the canine heart during normal atrioventricular transmission

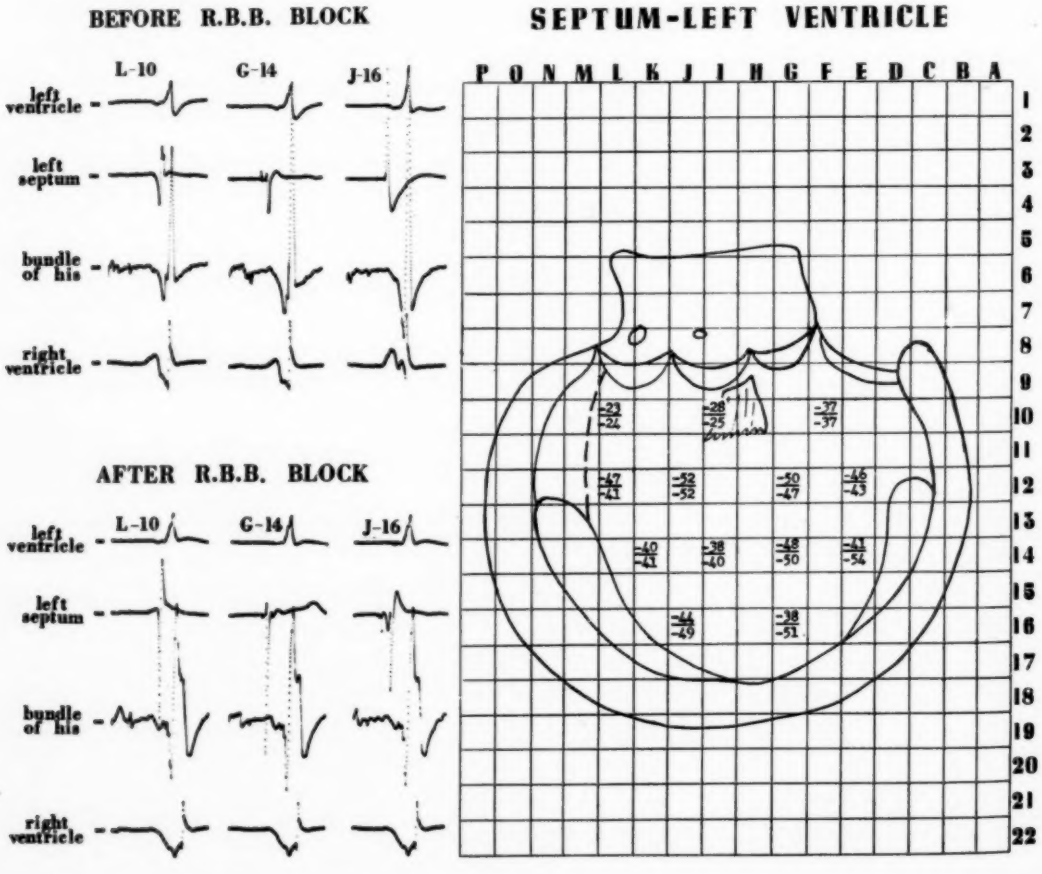


Fig. 8.—Activation of the left ventricular septal surface before and after RBBB. Numbers above the line were obtained before RBBB, and those below after RBBB. Reference tracings are from the left ventricle and the bundle of His. Note lack of delay at all points following RBBB.

and after production of either right or left bundle branch block. A major advantage of this open-heart technique is that recordings from many selected points can be obtained under direct vision without local injury. In addition, records can be obtained from both the earliest and latest points of activity on either septal surface.

The results of this study are in general agreement with previous reports with respect to the over-all sequence of activation of the septal surfaces. The earliest depolarization of septal muscle on the left is recorded from the central part of the left septal surface either above or below the midline; from this point, activity spreads to the apex and base. On the right side, earliest activity in septal muscle is recorded from the septum itself above and anterior to the anterior papillary muscle; from this point, activity spreads to the central and then to the basal and posterior parts of the right septal surface. These findings contrast with the results of others in that the anterior papillary muscle is not the site of earliest activity on the right side. In addition, the time of earliest activation on the right and left sides of the septum differed by no more than 1 to 2 msec. in any experiment. Failure of previous studies to reveal this almost synchronous appearance of activity on both sides of the septum most likely results from the relatively small area involved on the right in contrast to the large area on the left which is depolarized within a few milliseconds of the earliest activity. Several

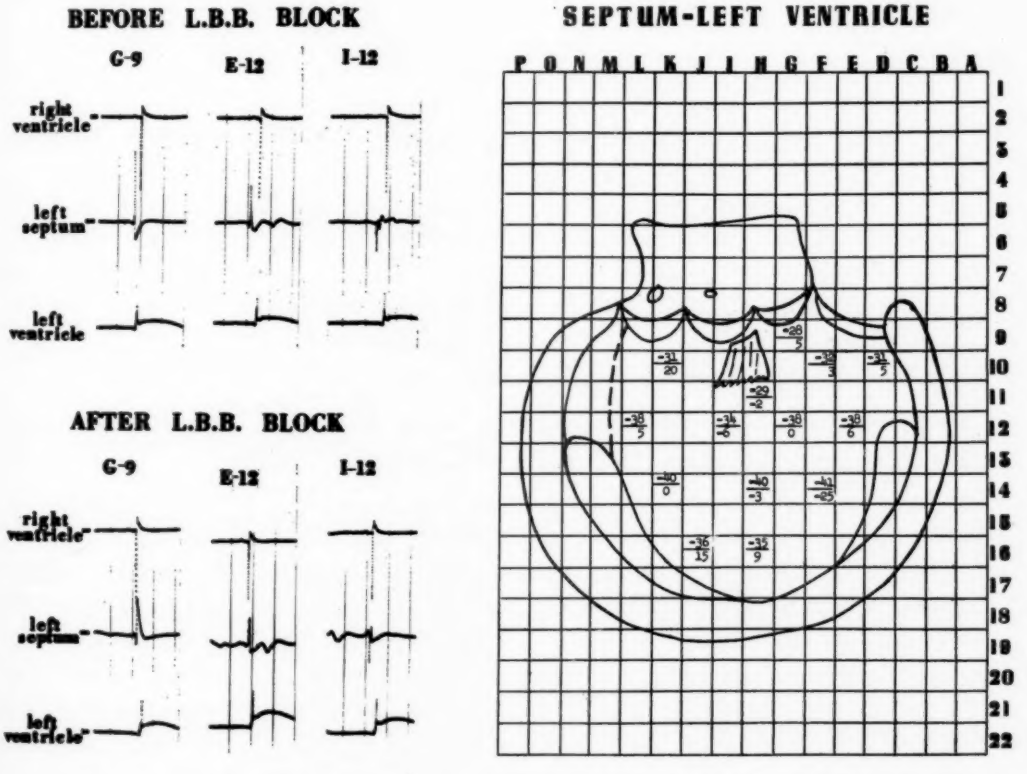


Fig. 9.—Activation of the left ventricular septal surface before and after LBBB. Numbers above the line were obtained before LBBB, and those below after LBBB. Reference tracings are from the right ventricle. Note delay at all points following LBBB.

investigators have stated that areas of the right septal surface were activated via the left bundle branch. Scher[6] concluded that the posterosuperior aspect of the right septum was dominantly or completely activated from the left bundle branch in 60 per cent of canine hearts. Sodi-Pallares[10] has stated that the base of the anterior papillary muscle of the right septal surface was probably formed by left ventricular tissue, since its activation vector was modified little or none when incomplete or complete right bundle branch block was produced. He also concluded that other

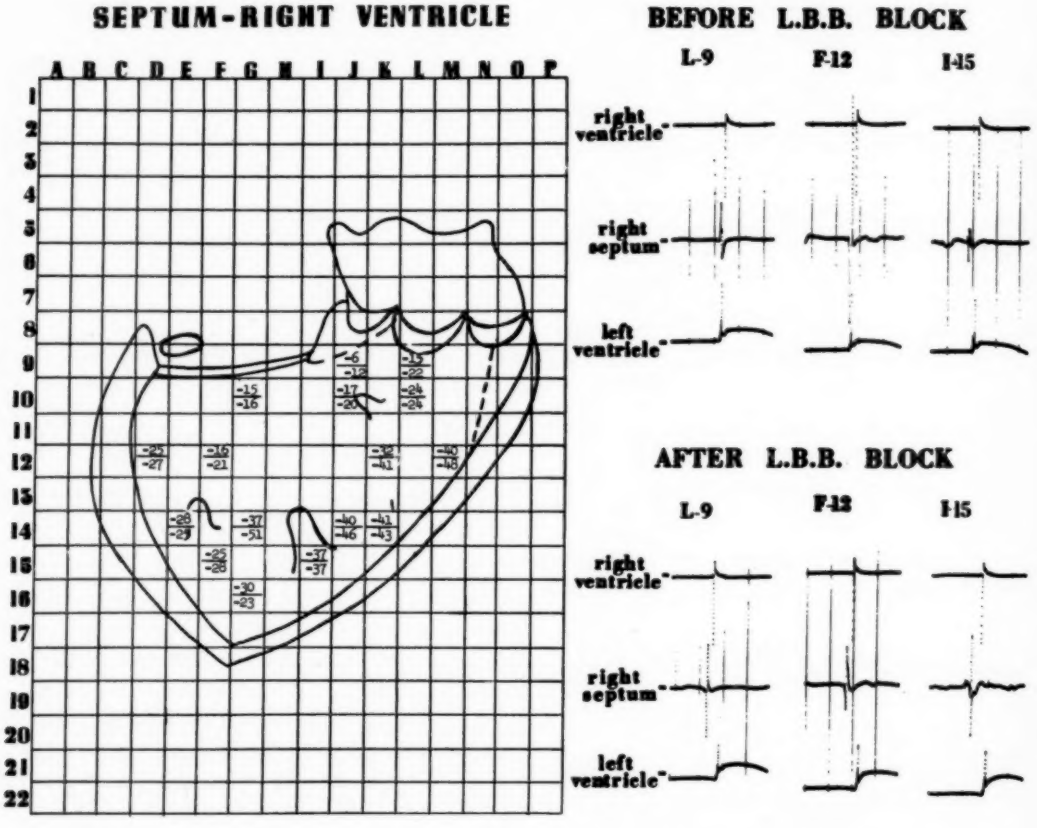


Fig. 10.—Activation of the right ventricular septal surface before and after LBBB. Numbers above the line were obtained before LBBB, and those below the line after LBBB. Reference tracings are from the right ventricle. Note absence of delay at all points following LBBB.

parts of the right septal surface were formed from left ventricular tissue in some animals. In the present investigation, surgically induced right bundle branch block resulted in delayed activation of the anterior and middle parts of the right septal surfaces, including the anterior papillary muscle, in all animals. The posterior and basal parts of the right surface showed delayed activation after right bundle branch block in some experiments and little or no change in the time of activation in others. Also, in one animal, left bundle branch block possibly caused some delay in the time of activation of the posterior part of the right septal surface. These findings support the conclusion that a part of the posterior aspect of the right surface is activated from the left bundle branch in some dogs.

Right bundle branch block caused no change in the time or sequence of activation of the left septal surface; left bundle branch block, as has been demonstrated by several investigators, caused delayed activation of the entire left surface. Following either right or left bundle branch block the sequence of activation of the affected side varied in different animals. This problem is the subject of further study.

SUMMARY

The sequence of activation of the right and left surfaces of the interventricular septum of the canine heart has been studied by means of bipolar electrograms recorded under direct vision from multiple selected points in the in situ heart during total cardiopulmonary bypass. Earliest activity is almost simultaneous on both sides of the septum; depolarization of septal musculature is first recorded, on the right, from the septum above and anterior to the anterior papillary muscle and, on the left, from the central septum either above or below the midline. Records of septal activation after bundle branch block show that all of the anterior and middle parts of the right surface, including the anterior papillary muscle, are dependent on the right bundle branch for normal activation, and all of the left surface is dependent on the left bundle branch. In some animals the posterior and basal parts of the right surface are normally activated from some part of the left bundle branch.

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Electrocardiographic Observations in 300 Transthoracic Left Heart Catheterizations

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Numerous observations have been reported on arrhythmias precipitated by right heart catheterization,[1-8] but no specific study has appeared so far on the electrocardiographic changes occurring during catheterization of the left side of the heart. The latter is now a well-established procedure in the accurate diagnosis of mitral and aortic valvular disease.[9-12]

In the past three years (1956-1959) in the Toronto General Hospital, left heart catheterization was attempted in 300 problem cases of valvular heart disease, using the right posterior transthoracic approach of Björk.[10] The procedure was successfully completed in 281 cases (93.6 per cent); there were no fatalities.

It is the purpose of this paper to review the electrocardiographic changes which occurred during and shortly after left heart catheterization.

MATERIAL AND METHODS

Of the 300 patients who underwent left heart catheterization, 141 were males and 159 were females. The age range was 14 to 66 years. The distribution according to type of heart disease is given in Table I.

The term "myocarditis," as applied to 8 cases in this series, was used to indicate the presence of elevated end-diastolic left ventricular or mean left atrial pressure in the absence of valvular disease.

The 2 cases of atrial septal defect represent errors in clinical diagnosis. These patients had been considered before catheterization to have mitral disease.

The patients with normal hemodynamic findings presented symptoms and clinical or radiographic signs suggestive of mitral or aortic valvular disease.

Left ventricular failure was present in 92 patients, right ventricular failure in 36, and combined right and left ventricular failure in 27. Two hundred and seventy-one patients were receiving digitalis prior to catheterization, and one was receiving quinidine.

The important electrocardiographic findings observed prior to catheterization are given in Table II.

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Preoperative sedation was induced with 50 to 100 mg. of meperidine hydrochloride (Demerol) and 3 grains of sodium Amytal one hour prior to catheterization. Five patients had general anesthesia.

The patient was placed in the left lateral position. A Björk type of needle (15 to 17 gauge) was inserted usually into the eighth right intercostal space and was advanced, with fluoroscopic guidance, into the left atrium, which had been outlined by a barium swallow.

The left atrium was entered in 289 cases. In 275 cases a small nylon or polyethylene catheter, threaded through the needle, was advanced across the mitral valve into the left ventricle and occasionally into the aorta. In 6 cases the needle entered the left ventricle. In 21 cases, two needles were inserted into the left atrium for assessment of mitral regurgitation by the indicator dilution technique. In 38 cases, combined left and right heart catheterization was done.

Standard Lead II or Lead III of the electrocardiogram was monitored during the procedure and for a 30-minute observation period following it.

TABLE I. FINAL DIAGNOSIS FOLLOWING LEFT HEART CATHETERIZATION IN 300 CASES

Mitral stenosis	49
Mitral insufficiency	42
Mitral stenosis and insufficiency	55
Mitral stenosis and tricuspid insufficiency	7
Aortic stenosis	43
Aortic insufficiency	7
Aortic stenosis and insufficiency	15
Mitral and aortic valvular disease	47
Myocarditis	8
Primary pulmonary hypertension	2
Atrial septal defect	2
Normal hemodynamic findings	23
Total	300

TABLE II. ELECTROCARDIOGRAPHIC FINDINGS PRIOR TO LEFT HEART CATHETERIZATION IN 300 CASES

Normal sinus rhythm	132
Nodal rhythm	2
Atrial fibrillation	160
Normal sinus rhythm with first degree A-V block	5
Complete A-V block	1
Right bundle branch block	11
Left bundle branch block	6
Right ventricular hypertrophy	42
Left ventricular hypertrophy	87
Combined right and left ventricular hypertrophy	125

RESULTS

Extrasystoles were the most common arrhythmia. They occurred in 199 cases (63.3 per cent) and were of atrial type in 22 and of ventricular type in 177. The atrial extrasystoles were usually sporadic and occurred more frequently when the tip of the catheter was lying within the ventricle (15 cases out of 22). In one case atrial bigeminy was noted. The ventricular extrasystoles were sporadic

in 77 cases, and in 71 they occurred in groups of three or more, constituting short bursts of ventricular tachycardia. Ventricular bigeminy was observed in 28 cases and ventricular parasystole in one.

In 119 out of 177 cases, ventricular premature beats were of QS or rS type, with upright T waves (Fig. 1,*B*). In 45 cases they showed a broad, notched, tall R wave with inverted T, and were similar to those usually encountered during catheterization of the right ventricle (Fig. 1,*A*) when a combined procedure was carried out. In the remaining 13 cases both types of extrasystoles were present. The different configuration of the extrasystoles suggested that the more common type, as in Fig. 1,*B*, arose from the left ventricle, and that the less common type (Fig. 1,*A*) arose from the right ventricle. Because only Lead II or Lead III was regularly recorded during the procedure, it was not possible to establish with certainty the ventricle of origin.

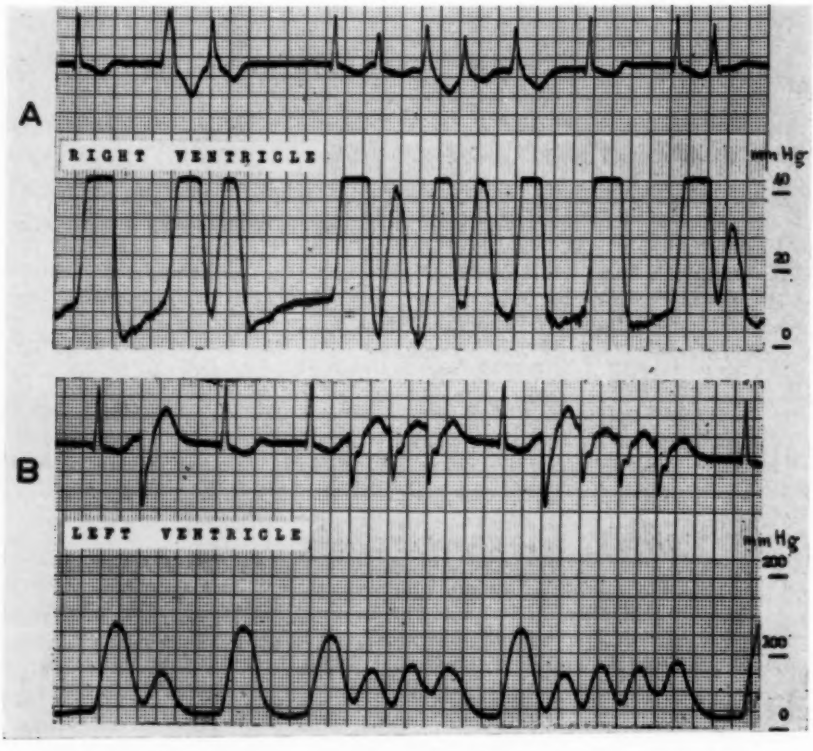

Fig. 1.—Ectopic beats of different morphology, occurring during catheterization of the right ventricle (*A*) and left ventricle (*B*) in a patient on whom a combined procedure was carried out.

Ventricular premature beats occurred most frequently when the catheter entered the ventricle, and they disappeared promptly when it was withdrawn into the atrial chamber (Fig. 2), or advanced into the aorta. Most of the ventricular ectopic beats occurred as soon as the tip of the catheter crossed the mitral ring and was lying within the inflow tract of the left ventricle.

In 19 cases (10.7 per cent), ventricular extrasystoles occurred also when the tip of the catheter was situated in the atrium (Fig. 3).

Arrhythmias with rapid ventricular action were observed in 44 patients. Twelve patients had sinus tachycardia (110 to 150 per minute), which did not interfere with the progress of cardiac catheterization. Four had paroxysmal atrial tachycardia which reverted to sinus rhythm either spontaneously (1 patient), by simple eye-ball or carotid sinus pressure (1 patient), or following digitalis therapy (2 patients). In one of the latter two patients the procedure had to be discontinued because of a disturbing rise in the left atrial pressure and distressing symptoms. Twenty-eight patients with established atrial fibrillation developed rapid ventricular rates (110 to 160 per minute), which resulted in pulmonary edema in 4 patients immediately after left heart catheterization. The rapid ventricular rate in this group of 28 patients was controlled by digitalis within 6 hours of the procedure.

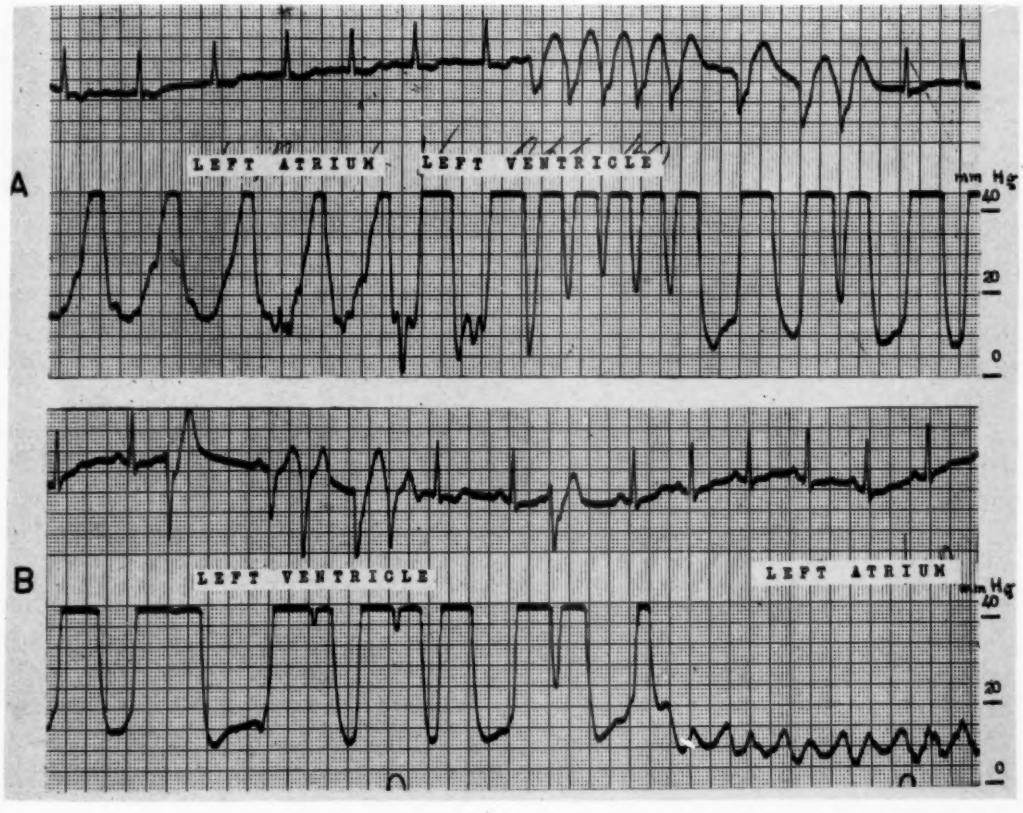

Fig 2.—*A*, Mitral insufficiency. Short burst of ventricular tachycardia occurring as soon as the catheter is advanced from the left atrium into the left ventricle. *B*, Normal mitral valve. Ventricular extrasystoles disappearing as soon as the catheter is withdrawn from the left ventricle into the left atrium.

Arrhythmias with slow ventricular rates appeared in 10 patients. Four patients had marked sinus bradycardia (40 to 50 per minute) (Fig. 3), one had sinus block with nodal escapes, one had complete atrioventricular block with a ventricular rate of 40, and four, who had established atrial fibrillation, had bradycardia (40 to 50 per minute).

Slow ventricular rates were often accompanied by sweating and hypotension (60 to 80 mm. Hg systolic); patients with such conditions recovered spontaneously within 1 or 2 hours of catheterization, or responded promptly to vasopressor agents (mephentermine sulfate, 60 mg. intramuscularly or intravenously) (4 patients). Marked bradycardia and hypotension were frequently associated with deep injections of local anesthetic (procaine hydrochloride 1 per cent) in the posterior mediastinum.

Less frequent arrhythmias were: coronary sinus rhythm (2 patients), nodal rhythm (4 patients), paroxysmal atrial fibrillation with well-controlled ventricular rate (4 patients).

Disturbances in the atrioventricular conduction occurred in 3 patients (1 per cent), with first-degree A-V block in two, and complete A-V block, which disappeared within 4 hours of catheterization, in one. One patient showed transient right bundle branch block. No instances of left bundle branch block were noted.

Minor changes in the S-T segment and T waves occurred during or following rapid ventricular rate or marked bradycardia.

The effects of ventricular premature beats on the atrial pressure and on the systolic and diastolic left ventricular pressures are shown in Fig. 4. The effects of ventricular premature beats on the pressure gradients across the aortic and mitral valves are shown in Fig. 5.

Changes in the pressure recordings were significant when frequent extrasystoles and rapid ventricular rates occurred. Rapid ventricular action was accompanied by an increased left atrial pressure, increased left ventricular diastolic pressure, decreased left ventricular systolic pressure (Fig. 6), and decreased aortic systolic pressure and pressure gradient across the aortic valve.

The occurrence of atrial paroxysmal tachycardia in a case of mitral insufficiency produced alternans in the ventricular (Fig. 7) and aortic pressure pulses.

The occurrence of arrhythmias made the pressure readings unreliable in 12 patients.

No relationship was found between incidence of extrasystoles and underlying disease, age, sex, digitalization of the patient, type of catheter used (nylon or polyethylene), and injections of dye. The two-needle procedure did not seem to precipitate arrhythmias more frequently than did the routine procedure. Rapid ventricular rate in case of established atrial fibrillation occurred more frequently (82 per cent of the cases) when the mean left atrial pressure was above 25 mm. Hg.

No electrocardiographic changes were noted in 85 cases (28.3 per cent).

COMMENT

In left heart catheterization, as in right heart catheterization, ectopic beats are the most common electrocardiographic disturbance, although the incidence is lower in this series (63.3 per cent) than that reported by others[2,6] during right heart catheterization (88 to 95 per cent).

Mechanical stimulation by the catheter and the Björk needle is the presumed cause. Ventricular ectopic beats, eight times more frequent than atrial, occur

when the catheter lies within the left ventricle and disappear promptly if the catheter is advanced into the aorta or withdrawn into the atrium. Occasionally, ventricular extrasystoles may occur when the tip of the catheter is lying in the atrium. A possible explanation is that while the tip of the catheter is situated within the atrial chamber, the rest of it may loop across the mitral valve into the left ventricle and stimulate the left ventricular wall. Observations during repeated passages of the catheter across the mitral and aortic valves strongly suggests that the most irritable part of the left ventricle is that surrounding the atrioventricular ring.

Atrial ectopic beats occur independently of the position of the catheter and most likely are precipitated by the Björk needle, which has pierced the atrial wall and is kept in situ throughout the procedure.

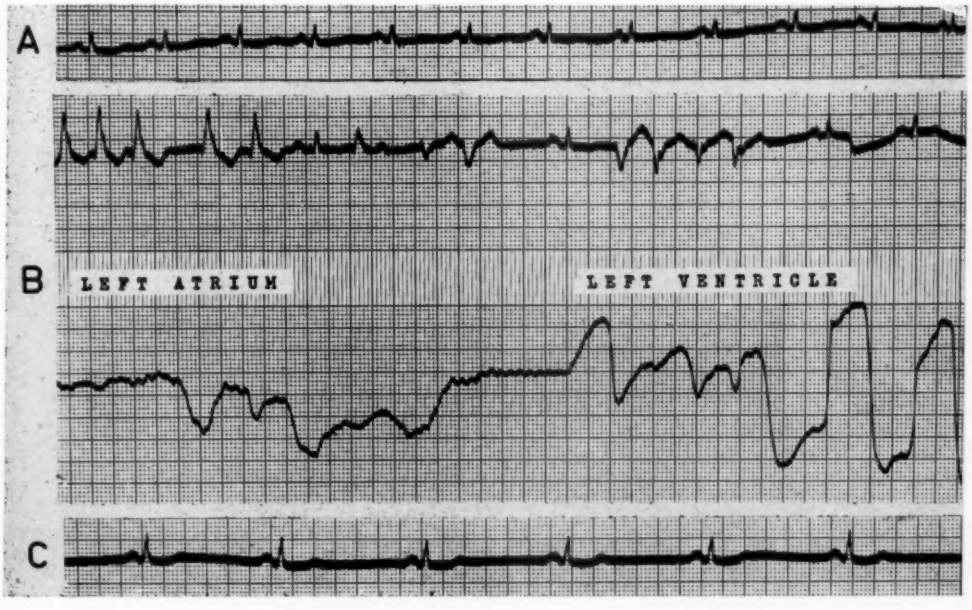

Fig. 3.—*A*, Precatheterization electrocardiogram. *B*, Ectopic beats of different morphology occurring while the catheter is lying within the left atrium or is being advanced into the left ventricle. *C*, Postcatheterization bradycardia.

Atrial premature beats and sporadic ventricular beats may be disregarded during left heart catheterization. Ventricular extrasystoles, when occurring in groups of three or more, should be avoided by changing the position of the catheter within the ventricle or withdrawing it into the atrium. Runs of ventricular ectopic beats alter the pressure readings significantly (Fig. 4) and may progress into persisting ventricular tachycardia, flutter or fibrillation, as reported by various authors during right heart catheterization.[2,4,6,8]

Paroxysmal atrial tachycardia is uncommon during left heart catheterization. In this series it occurred in 1.3 per cent of the cases, and in only one did it interfere with the completion of the procedure, since it failed to respond promptly to the usual treatment (carotid sinus pressure, Prostigmin, digitalis). It is of interest to

observe that this arrhythmia occurs almost with the same frequency during right heart catheterization in the group with acquired valvular disease,[5] whereas it is more frequent (11 to 14 per cent) in the group with congenital heart disease.[2,5,8]

Paroxysmal atrial fibrillation is not frequent (1.3 per cent of the cases) and usually occurs when the left atrial pressure is elevated. This arrhythmia was accompanied by a well-controlled ventricular rate (below 100 per minute) and did not require treatment.

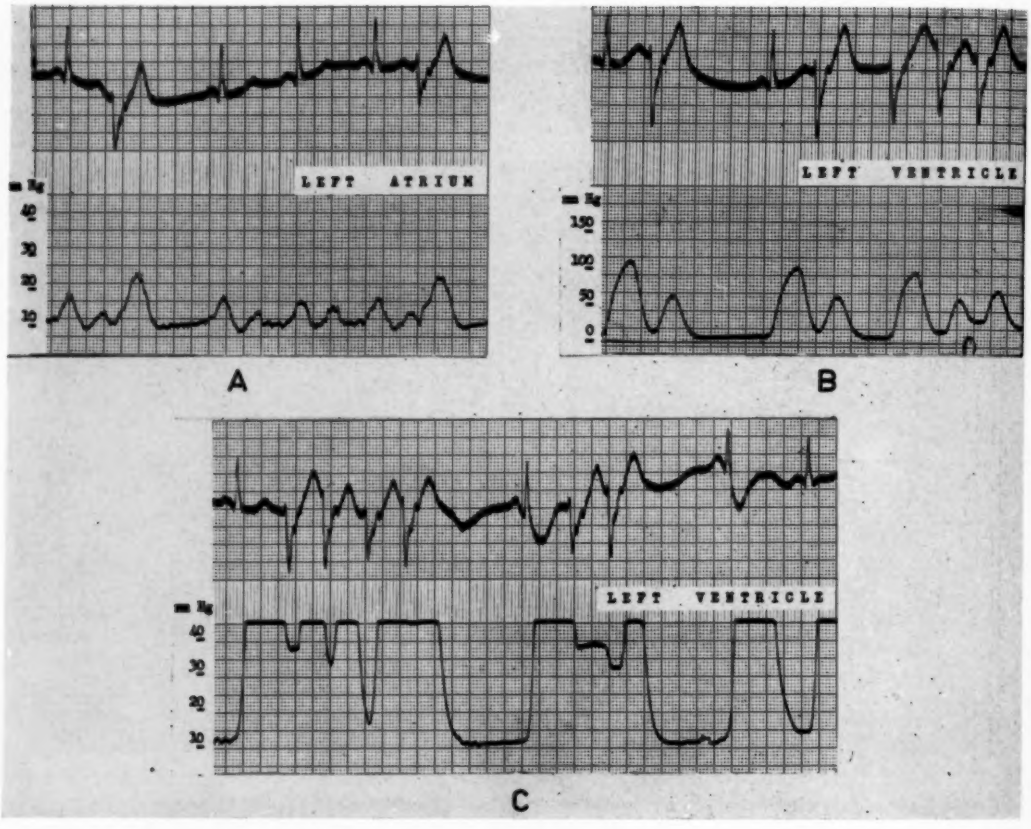

Fig. 4.—Effects of isolated and grouped ventricular extrasystoles on: *A*, the left atrial pressure; *B*, the systolic left ventricular pressure; *C*, the diastolic left ventricular pressure. When premature ventricular contraction occurs, the atrial pressure increases because the atrial discharge is baffled; the systolic ventricular pressure decreases because of reduced ventricular filling; the diastolic ventricular pressure increases because of incomplete ventricular discharge.

Patients with established atrial fibrillation may develop a rapid ventricular rate (110 to 160 per minute), as occurred in 28 cases in this series. This arrhythmia is of importance, not only because of the potential development of pulmonary edema in patients with severe valvular disease, but also because of the effect of the rapid ventricular rate on the pressure tracings leading to possible errors in interpretation. It has not been our practice to give additional digitalis in these instances because of the possibility of increasing ventricular irritability, but rather to complete the necessary records as quickly as possible.

Bradycardia (40 to 50 per minute) may occur both in patients with sinus rhythm and in patients with established atrial fibrillation. Bradycardia is not frequent (less than 3 per cent of the cases) and is often associated with hypotension. The impression was gained early in the series that this arrhythmia was produced by large injections of local anesthetic in the posterior mediastinum. For this reason, injections of procaine were thereafter made only as far as the periosteum of the thoracic vertebrae, in an attempt to avoid infiltration of the cardiac plexus. This change in the technique did not noticeably increase the patients' discomfort and made bradycardia less frequent and severe.

Transient coronary sinus and nodal rhythms are rare and unimportant. They appeared in 2 per cent of the cases, an incidence (1.5 per cent) similar to that reported during right heart catheterization.[5]

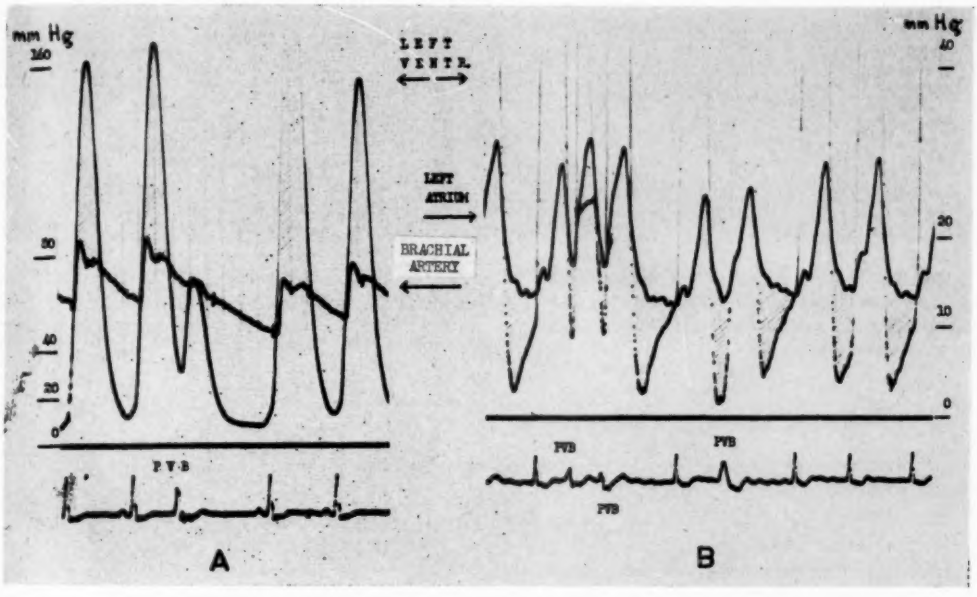

Fig. 5.—*A*, Simultaneous pressure recordings from the left ventricle and brachial artery in a patient with aortic stenosis. There is a gradient of about 80 mm. Hg across the aortic valve, which disappears with the occurrence of a premature beat. *B*, Simultaneous pressure recordings from the left atrium and left ventricle in a patient with mitral stenosis and insufficiency. Note the effect of premature beats on the pressure gradient across the mitral valve.

Rare but disturbing arrhythmias are transient sinus block with nodal or ventricular escapes and transient complete A-V block. The mechanism of these is uncertain. Each occurred only once in this series. On each occasion the procedure was quickly completed. Normal sinus rhythm and normal A-V conduction reappeared within 4 hours.

Transient right bundle branch block is extremely rare (0.33 per cent) as compared with its incidence in right heart catheterization, during which it occurs in 5 to 14 per cent of the cases.[2,5,7] Left bundle branch block did not occur.

Mechanical compression of the right bundle by the catheter is the probable cause of the transient bundle branch block during right heart catheterization.[17]

The anatomic position of the left bundle, which is situated more deeply in the interventricular septum than is the right bundle, and the softness of the plastic tubing used in left heart catheterization probably account for the absence of left bundle branch block during left heart catheterization.

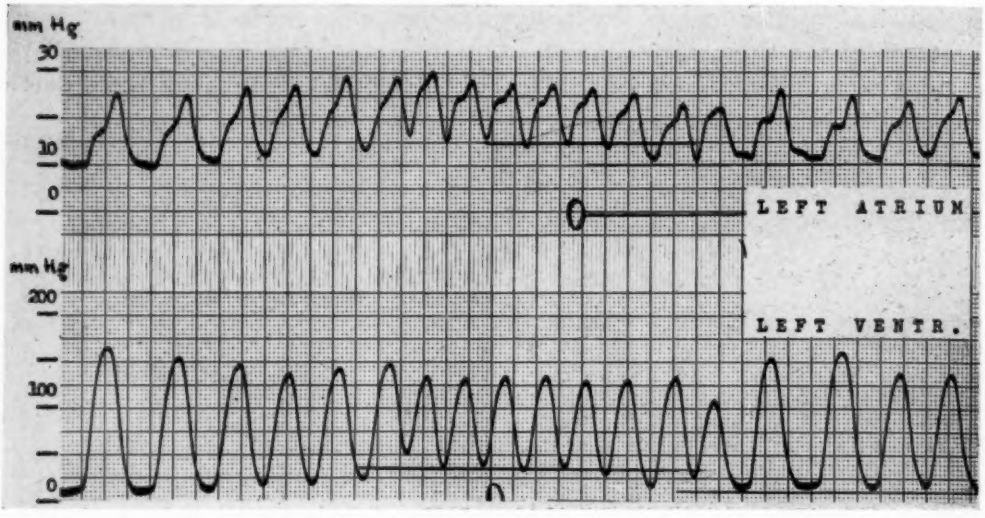

Fig. 6.—Simultaneous pressure recordings from the left atrium (*upper tracing*) and the left ventricle (*lower tracing*) in a patient with mitral valvular disease. With the occurrence of a rapid heart rate the left atrial and the diastolic left ventricular pressures increase, whereas the systolic left ventricular pressure decreases.

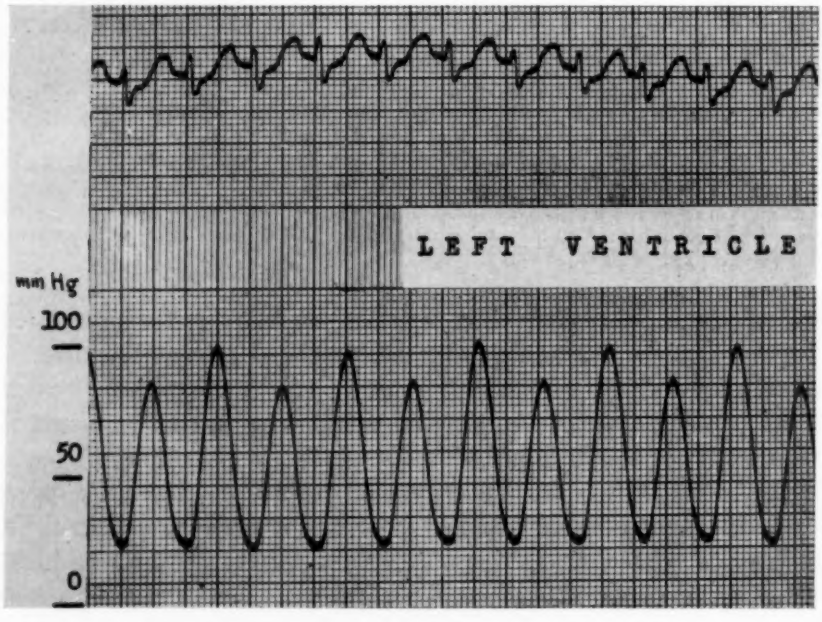

Fig. 7.—Patient with mitral insufficiency. The left ventricular pressure pulse shows a striking alternance during an episode of paroxysmal atrial tachycardia.

Pre-existing left bundle branch block has been considered a contraindication to right heart catheterization,[5,6] in view of the frequent occurrence of right bundle branch block during this procedure which may transform it into a complete A-V block. Pre-existing bundle branch block of either type is not a contraindication to left heart catheterization because of the small incidence of intraventricular conduction defects during the procedure.

In this series there have been no cases of ventricular tachycardia, flutter, fibrillation, or cardiac standstill. However, Bagger and associates,[15] in a series of 167 left heart catheterizations, reported three cases of ventricular fibrillation, two associated with cardiac tamponade and one with angiocardiography. They reported also one case of transient cardiac standstill during left heart angiocardiography. These four serious arrhythmias followed either a complication or a supplementary procedure.

No serious arrhythmias have been reported in other series of left heart catheterizations.[10,11,14,16,18,19]

There is no apparent relationship between the incidence of arrhythmias and the age and sex of the patient, digitalization or presence of heart failure. The underlying disease may occasionally be a predisposing factor. In mitral valvular disease the elevated left atrial pressure may increase the possibility of paroxysmal atrial fibrillation or, if atrial fibrillation is already established, of rapid ventricular rates.

Changes in repolarization during left heart catheterization are transient and secondary to disorders of the heart beat.

SUMMARY

Left heart catheterization by the right posterior transthoracic approach of Björk precipitates arrhythmias less frequently than does right heart catheterization.

In this series of 300 consecutive left heart catheterizations no cases of ventricular tachycardia, fibrillation, cardiac standstill, or persistent complete A-V block were observed.

Atrial and ventricular ectopic beats occurred in 63.3 per cent of the cases, paroxysmal atrial tachycardia in 1.3 per cent, rapid ventricular rate in established atrial fibrillation in 9.3 per cent, bradycardia in 2.6 per cent, nodal or coronary sinus rhythm in 2 per cent, and transient complete A-V block in 0.3 per cent.

There was only one case of transient right bundle branch block and no case of left bundle branch block. Pre-existing bundle branch block does not contraindicate the procedure.

Age of the patient, digitalization, presence of cardiac failure do not predispose to a higher incidence of arrhythmias during left heart catheterization.

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A Geometric Study of the Relationship Between Limb Leads and Cardiac Vector in the Frontal Plane

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Over ten years ago, Wilson in this country and Burger in the Netherlands developed almost simultaneously an important concept in the theory of electrocardiography. The fundamentals of this concept may be expressed in an algebraic equation which indicates that the differences in potentials recorded in any body surface lead are linearly related to the sum of the three cardiac vector components, x, y, z, and each component bears a constant. These constants may be obtained from actual experimental measurements, using torso model, phantom, or other means.

The great advantage of this concept of lead vector over the common spatial counterpart of the Einthoven assumption is that the concept enables us to obtain the cardiac vector with great accuracy from body surface leads irrespective of thorax shape, heterogeneous medium, and eccentric location of the cardiac vector. In fact, these properties are incorporated in the constants. Similar concepts exist at the present time, namely, the lead-field concept and the transfer-impedance concept.

For the past few years we have been interested in and have participated in these matters, particularly in the theoretical and practical development of spatial vectorcardiographic systems. At the same time we had in mind that a geometric study of the theoretical aspects could be very instructive. This is justified because of the fact that, in general, simple geometric figures are more accessible to us physicians than are any other mathematical means. Since the situation in space may be extended from a two-dimensional consideration, we have, for the sake of simplicity, limited our geometric representations to one plane. We have chosen the RLF plane for our study because this plane is familiar to us all.

The first geometric figure in this regard is a scalene triangle for the RLF plane, constructed several years ago by Burger and van Milaan. The present paper contains altogether five sections devoted to geometric representations.

The experiments were performed at the medical schools of the University of São Paulo, São Paulo, Brazil, and the University of Texas, Galveston, Tex.

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These are not limited only to scalene triangles with different configurations, but include as well other geometric forms, namely, comparative curves and multiple radii with circles. We have constructed these latter forms in an attempt to facilitate comparative studies between the Einthoven assumption and the present

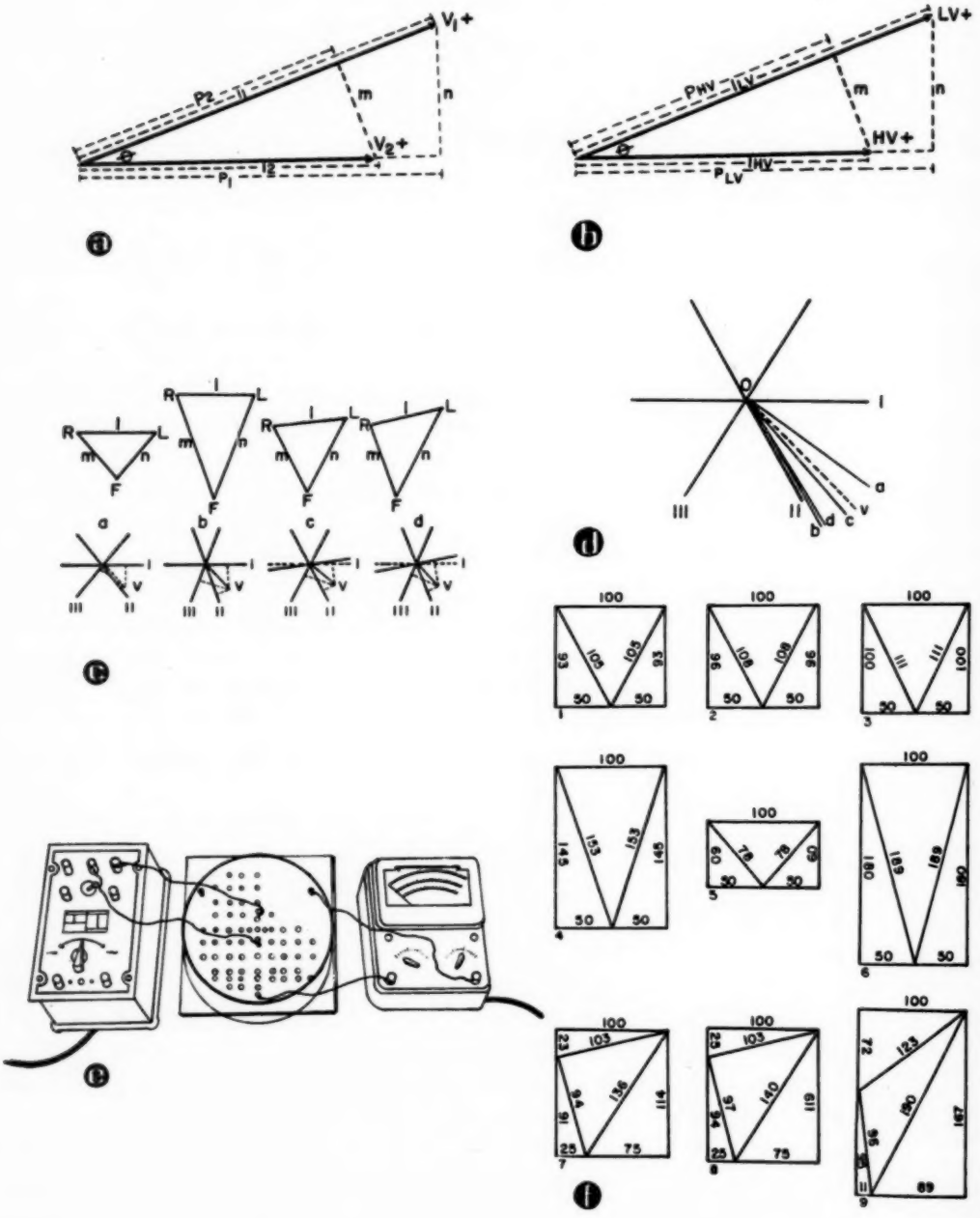

Fig. 1.—*a*, The scalar product of two vectors, V_1 and V_2. *b*, An ECG deflection is the scalar product of lead vector and heart vector. *c*, Four hypothetic Burger triangles with corresponding triaxial reference systems. *d*, Directions calculated in the Einthoven triangle deviate from the true ones. *e*, An RLF-plane electrolytic model. *f*, The Burger triangle in various shapes as a consequence of heart vector position (centric and eccentric) and length. (After Zao.[36,37])

concept. All the geometric configurations are based upon experimental data, mostly from studies with an electrolytic model as well as by means of living toad hearts in situ as recently developed in our laboratory.

I. THE RELATIONSHIP BETWEEN BURGER TRIANGULAR SHAPES AND THE EINTHOVEN TRIANGLE

The Burger triangle from a given subject (human or animal, living or dead, or electrolytic model) could have one of three shapes: equilateral, isosceles, or scalene. If it is equilateral, which is exceptional, the Einthoven triangle is obviously accurate. If it is not equilateral, the Einthoven triangle is inaccurate. But isosceles or scalene triangles can have various accentuations and departures from the equilateral triangle.

Fig. 1,*c* shows four hypothetical Burger triangles from four subjects; *a* and *b* are isosceles, whereas *c* and *d* are scalene. But *b* and *d* depart more from the equilateral than do *a* and *c*. For convenience, a Burger triangle may be transformed to a triaxial reference system (just as the Einthoven triangle has been transformed to the triaxial reference system of Bayley), with parallel transposition of the three sides toward its geometric center until they coincide. Four such triaxial reference systems, transformed from triangles *a*, *b*, *c*, and *d*, are shown directly beneath the triangles. Let l, m, n = length of bipolar limb lead vectors 1, 2, 3; p_1, p_2, p_3 = projections of heart vector upon l, m, n. By definition of lead vector concept, bipolar limb leads L1, L2, and L3 are expressed as: L1 = lp_1, L2 = mp_2, L3 = np_3.

In order to demonstrate the relationship between the Burger triangular shapes from Fig. 1,*c* and the inaccuracy of the Einthoven triangle, it is necessary to assume the heart vector to be of equal length in the same arbitrary direction, V (+45°), in each case. From the terminus of V in each triaxial reference system, perpendicular lines to the three sides were drawn; p_1, p_2, and p_3 were measured. From the above equations the deflections in L1, L2, and L3 were calculated. The values were used to plot the vectorial direction for each subject in the triaxial reference system of Bayley (Fig. 1,*d*). The directions *a*, *b*, *c*, and *d* were from subjects with Burger triangles *a*, *b*, *c*, and *d*, respectively. It may be observed that they deviate from V; that ∠ boV is larger than ∠ aoV, and that ∠ doV is larger than ∠ coV.

Thus the Einthoven triangle is inaccurate for subjects possessing Burger triangles either of scalene or isosceles shape. The more the triangle departs from the equilateral, the more the vectorial direction, calculated in the Einthoven triangle, deviates from the true one.

II. AN ELECTROLYTIC MODEL STUDY: BURGER TRIANGLE AS A QUANTITATIVE MEASURE OF THE INACCURACY OF EINTHOVEN TRIANGLE, INFLUENCED BY "HEART VECTOR" ECCENTRICITY AND LENGTH

Fig. 1,*e* shows the experimental arrangement. At the center of this figure is shown a covered, low cylindrical glass of 20 cm. in diameter, filled with tap water. The cover contained several holes, each being about 3 mm. in diameter. These

served for the introduction of electrodes to make contact with the surface of the water. The surface of the water represented the RLF plane. Two electrodes leading from an AC source (left of the figure) were introduced through the holes to contact the surface of the water, simulating two poles of the "heart vector." In each experiment a definite position and a definite length between the two poles were used. Three bipolar limb leads were taken with the two poles horizontally directed, and these leads were repeated when the two poles were vertical. The three bipolar limb leads were connected from three electrodes, R, L, and F, which had been introduced in contact with the surface of the water through proper openings at the corners. Differences in potentials in these leads were measured by a voltmeter (right of the figure) in decivolts.

In the present experiments the influence of the length and position of the two poles, particularly the eccentricity, upon the inaccuracy of the Einthoven triangle was considered. The RLF plane was assumed to be a homogeneous circular disc.

From the above measurements, Burger triangles were constructed by the graphic method described by Wilson and associates. Measurements were given on the proper sides, so that the construction is self-evident (Fig. 1,*f*).

Triangles 1, 2, 3, and 4.—The midpoint of the assumed "heart vector" was put in the central position in all cases. The length between the two poles was 2 cm. in 1, 4 cm. in 2, 12 cm. in 3, and 16 cm. in 4. All triangles were isosceles, because the limb electrodes were not at a great distance from the "dipole," which was always arranged to be equidistant from R and L but not at the same distance from F as from R and L. Indeed the departure from the equilateral was increased from 1 to 4. The Einthoven triangle was inaccurate in these cases; the greater the distance between the two poles, the more inaccurate was the Einthoven triangle.

Triangles 5 and 6.—The midpoint was put in an eccentric position. In 5 it was 2 cm. away from the center in the $-90°$ direction; in 6 it was 2 cm. away from the center in the $+90°$ direction. The length was 4 cm. in each case. Both triangles were isosceles; 5 was broad at the base, 6 was narrow at the base. The Einthoven triangle gave inaccurate results in both cases. Moreover, the departure from the equilateral was larger in triangle 6 than in triangle 5; consequently, the Einthoven triangle was more inaccurate for 6 than for 5. It appears that the inaccuracy of the Einthoven triangle, other factors being equal, depends not solely on the distance between the eccentric position and the geometric center, but on the eccentric position itself.

It is interesting to compare triangle 2 with triangle 5. The triangle is slightly narrow in the base in 2 and broad in the base in 5. In both triangles the length between the two poles was 4 cm. In 2 it was in the centric position, in 5 it was in the eccentric position, 2 cm. away from the center in the $-90°$ direction. As the triangles changed from a narrow base to a broad base, there was within this 2-cm. length an eccentric position which gave an equilateral Burger triangle. Consequently, the Einthoven triangle would be accurate for this instance.

Triangles 7, 8, and 9.—In each of these triangles the midpoint of the two poles was put in an eccentric position. In 7 and 8 it was at 2 cm. from the center

in the 0° direction, with a 4-cm. length between the two poles in 7, and an 8-cm. length in 8. In 9 the midpoint was 4 cm. from the center in the 0° direction and the length was 4 cm. These triangles were all scalene with lead vector 3 longer than lead vector 2. But triangle 9 departs more from the equilateral than does triangle 8. Thus, the inaccuracy of the Einthoven triangle was more affected by positions of the midpoint than by the length between the two poles.

III. DIRECT CONSTRUCTION OF BURGER TRIANGLES FROM LIVING TOAD HEARTS IN SITU AND THE SIMILARITY OF R AND T TRIANGLES FROM SAME TOADS

The principle of the Wilson method may be used to construct Burger triangles directly from living toad hearts in situ (Fig. 2,*a*). We proceeded as follows: (1) Destroy the central nervous system of the toad as usual. (2) Place the toad in a recumbent position on a cork board. Fix each leg with a German silver needle electrode on the board. Connect each electrode to a proper limb cable of an electrocardiograph. (3) Open the thorax, expose the heart and mobilize the two aortas. Fix the heart in different positions by a rod over the aortic bifurcation. (4) Place a twine ligature around the apex. Allow 10 minutes for the injury current to disappear. (5) Fix the heart vertically toward the +90° direction by means of the twine (*v*). Take the three standard ECG limb leads with normal speed and standardization (Fig. 2,*b*). (6) Fix the heart horizontally toward the 0° direction (*h*). Again take the three standard limb leads with the same normal speed and standardization (Fig. 2,*b*).

The ventricle of the toad is extremely symmetrical, and it was assumed that R peaks from the standard limb leads were practically synchronous in time. Similarly, the electrical axis and anatomic axis of the heart appeared identical in direction. Should slight directional deviation between the two axes in the same heart occur, configuration of the constructed scalene triangle remained unchanged, whereas its orientation might deviate slightly.

Three illustrative cases from toads A, B, and C are shown in Fig. 2,*c*. The numerical values are in millivolts, and were actually measured from toads' electrocardiograms (Fig. 2,*b*). Tracing *v* was taken with the cardiac apex pointing toward +90°, whereas tracing *h* was taken with the apex toward 0°. From both tracings of a given limb lead, amplitudes of R or T were measured in order to draw vertical and horizontal segments with relative positions determinable by polarities of R or T. The two segments formed the perpendicular sides of a right triangle whose hypotenuse represented the lead vector of that given lead for R or T. On the top row of Fig. 2,*c* are the triangles of R peak from toads A (left) and B (right); on the lower row the triangles of R peak (left) and of T peak (right) from toad C. It was shown elsewhere that Burger triangles gave accurate results and that the Einthoven triangle gave inaccurate results under these experimental conditions.

However, it should be mentioned that these triangles resemble those of Wilson and associates, constructed from a current dipole on the living human thorax. When the toad's heart was in its original position, the triangle was usually slightly scalene, lead vector 3 was larger than lead vector 2, and the angle between the lead vector 1 and the horizontal was negative. When the toad's heart was

fixed to the left of its original position at the same horizontal level, the triangle was of the same general configuration, except that it was more scalene; the more the heart was shifted to the left the more this was accentuated. When the heart was fixed to the right of its original position at the same horizontal level, lead

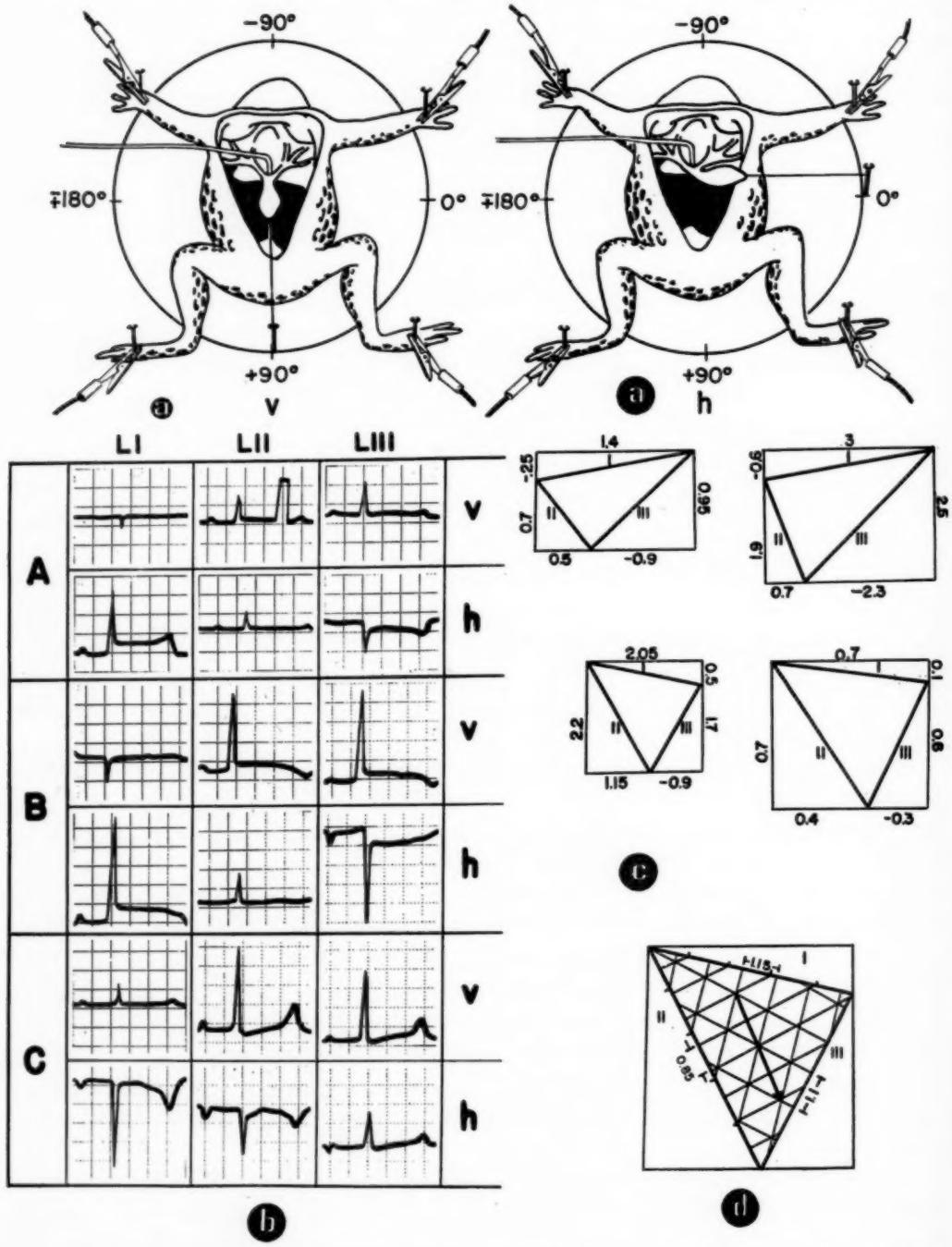

Fig. 2.—*a*, A method of constructing Burger triangles directly from living toad hearts in situ. *b*, The bipolar limb leads of toads A, B, and C. *c*, Four Burger triangles pertaining to toads. *d*, The Burger triangle with coordinate network. (After Zao.[44])

vector 2 was larger than lead vector 3, and the angle that defined the direction of lead vector 1 was positive.

The German physiologist Schaefer proposed the hypothesis that QRS and T vectors from the same human subject should be different in length and occupy different regions in the heart. If this were applicable to toads, triangles of R and T peaks of the same toads ought to be different. But they were almost identical in shape. Slight variations may be well within the limits of experimental errors. Therefore, Schaefer's hypothesis could not be confirmed experimentally, at least not on toads.

IV. THE BURGER TRIANGLE WITH COORDINATE SCALES

According to Brody, a Burger triangle may be provided with coordinate scales. It has interesting features as well, as shown below. Using the R peak triangle from toad C, we constructed the coordinate scales with a modified technique as follows (Fig. 2,*d*): (1) Divide lead vector 1 arbitrarily into 5 equal parts by four marks on it, as shown. From these marks draw perpendicular lines to lead vector 2. Add further parallel lines at equal interspacing in order to complete the sectioning of the triangle. The space between any two neighboring perpendicular lines on lead vector 2 equals one division for lead vector 2. (2) Divide lead vector 2 also into 5 equal parts with four marks on it. From these marks draw perpendicular lines to lead vector 1. Add further parallel lines at equal interspacing in order to complete the sectioning of the triangle. The space between any two neighboring perpendicular lines on lead vector 1 equals one division for lead vector 1. (3) Draw perpendicular lines to lead vector 3 in such a way that they intersect the meeting points of perpendicular lines to lead vectors 1 and 2. The space between any two neighboring perpendicular lines on lead vector 3 equals one division for lead vector 3.

The relative length of divisions for lead vector 1: lead vector 2: lead vector 3 is as 1.05:0.85:1.1 in this case. The arrow represents a given heart vector. The scalene triangle with coordinate scales has the following features: (1) It obeys the Einthoven law, L1 and L3 = L2, or 2 + 2 = 4 in the present case. (2) It synthesizes a set of instantaneous scalar lead data into a heart vector within the triangle. (3) Or conversely, the heart vector projects on the sides of the triangle so as to yield a set of scalar extremity leads.

V. TWO DIAGRAMS THAT GIVE SIMULTANEOUS RESULTS FROM EINTHOVEN TRIANGLE AND "AVERAGE" BURGER TRIANGLE

By the use of the method described in the previous section it was found that the relative length of the Brody division for lead vector 1 to lead vector 3 of the original Burger triangle obtained by Burger and associates from phantom measurements is as 2.2 to 1.0. The positive direction of lead vector 1 was measured as $-18°$, of lead vector 3, $+106°$.

A biaxial reference figure was made from the above data; divisions were measured in centimeters. An assumed heart vector of 10 cm. in length, originating from the bisection point of the biaxial figure, was rotated around the RLF plane.

At each 5-degree interval the orthogonal projections on lead vectors 1 and 3 were measured in terms of divisions, from which the quotient was calculated. Likewise, quotients were obtained for the Einthoven triangle by means of data from limb leads 1 and 3. Both results are given in Table I.

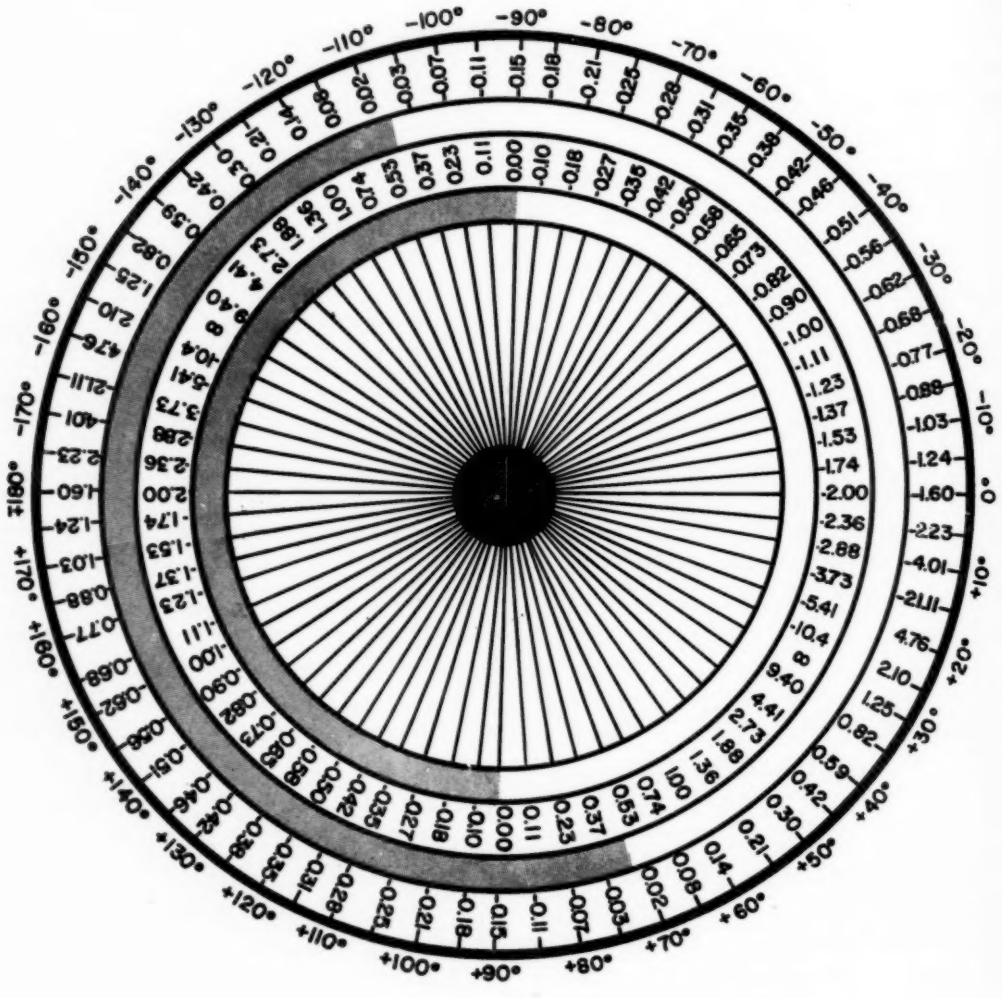

Fig. 3.—Diagram A.

The diagram A (Fig. 3) consists of, from without inward in circular arrangement, (1) the conventional RLF plane directions, (2) quotients valid for the Burger triangle, (3) the polarity circle of lead vector 1, (4) quotients valid for the Einthoven triangle, and (5) the polarity circle of lead 1. The heart vector center, shown as a black spot, together with 72 radical segments are also indicated. Each polarity circle consists of one positive semicircle (white), one negative semicircle (stippled), and two zero potential (or transitional) boundaries.

Let e_1 = any recorded deflection (P, QRS, ST, or T) in lead 1, mean, main or instantaneous; e_3 = corresponding deflection in lead 3. This diagram may be used as follows: Note the polarity of e_1. If it is positive, the direction is within the

positive semicircle of the polarity circle; if negative, it is within the negative semicircle. This holds true both for the polarity circle of lead 1 and lead vector 1. Calculate the quotient e_1/e_3, and then correlate this value in the respective semicircle to the direction that is valid for the Einthoven triangle and to the direction that is valid for the Burger triangle. (Exceptionally, e_1 may be zero potential. The direction is $+90°$ in the Einthoven triangle and $+72°$ in the Burger triangle when e_3 is positive; when e_3 is negative, the respective directions are $-90°$ and $-108°$.)

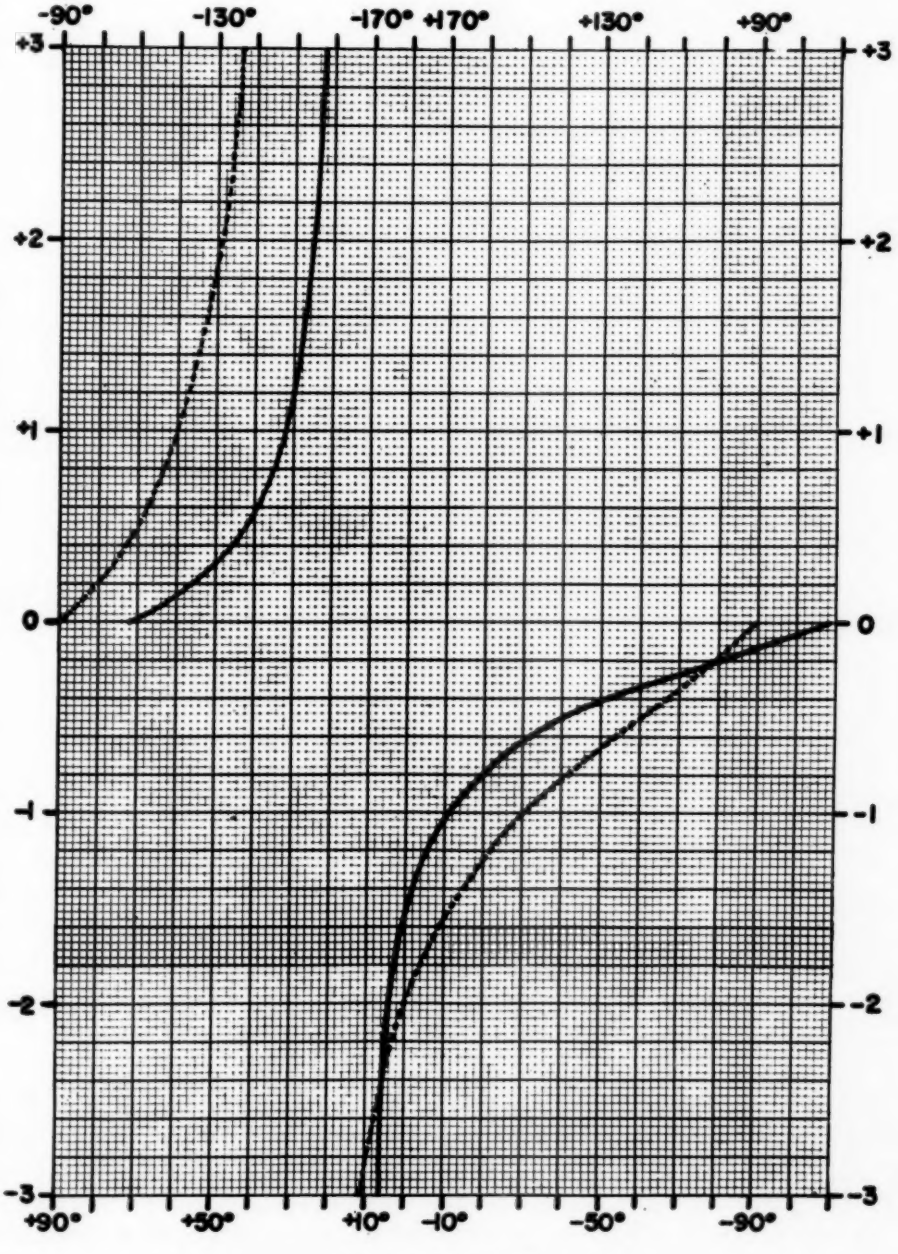

Fig. 4.—Diagram B.

Example 1.—If ÂQRS is −1 Ashman unit in lead 1 and +2.4 Ashman units in lead 3, to find the direction of ÂQRS in the Burger triangle and in the Einthoven triangle, proceed as follows: Since it is negative in lead 1, the direction is within each negative semicircle. The quotient −1/+2.4 equals −0.42. This value corresponds with +115° in the Einthoven triangle and +130° in the Burger triangle.

TABLE I. NUMERICAL DATA OF DIAGRAMS A AND B

RLF PLANE DIRECTIONS	E_1 ON LEAD 1	E_3 ON LEAD 3	QUOTIENT E_1/E_3 VALID FOR EINTHOVEN TRIANGLE	E_1 ON LEAD VECTOR 1	E_3 ON LEAD VECTOR 3	QUOTIENT E_1/E_3 VALID FOR AVERAGE BURGER TRIANGLE
0° ∓ 180°	10.0(+ −)	5.00(− +)	−2.00	4.32(+ −)	2.70(− +)	−1.60
+5° −175°	9.96(+ −)	4.23(− +)	−2.36	4.19(+ −)	1.88(− +)	−2.23
+10° −170°	9.85(+ −)	3.42(− +)	−2.88	4.01(+ −)	1.00(− +)	−4.01
+15° −165°	9.66(+ −)	2.59(− +)	−3.73	3.80(+ −)	0.18(− +)	−21.11
+20° −160°	9.40(+ −)	1.74(− +)	−5.41	3.57(+ −)	0.75(+ −)	+4.76
+25° −155°	9.06(+ −)	0.87(− +)	−10.40	3.31(+ −)	1.58(+ −)	+2.10
+30° −150°	8.66(+ −)	0.00	∞	3.03(+ −)	2.43(+ −)	+1.25
+35° −145°	8.20(+ −)	0.87(+ −)	+9.40	2.72(+ −)	3.30(+ −)	+0.82
+40° −140°	7.66(+ −)	1.74(+ −)	+4.41	2.40(+ −)	4.10(+ −)	+0.59
+45° −135°	7.07(+ −)	2.59(+ −)	+2.73	2.06(+ −)	4.88(+ −)	+0.42
+50° −130°	6.43(+ −)	3.42(+ −)	+1.88	1.69(+ −)	5.60(+ −)	+0.30
+55° −125°	5.74(+ −)	4.23(+ −)	+1.36	1.33(+ −)	6.23(+ −)	+0.21
+60° −120°	5.00(+ −)	5.00(+ −)	+1.00	0.95(+ −)	6.90(+ −)	+0.14
+65° −115°	4.23(+ −)	5.74(+ −)	+0.74	0.56(+ −)	7.50(+ −)	+0.08
+70° −110°	3.42(+ −)	6.43(+ −)	+0.53	0.17(+ −)	8.05(+ −)	+0.02
+75° −105°	2.59(+ −)	7.07(+ −)	+0.37	0.24(− +)	8.55(+ −)	−0.03
+80° −100°	1.74(+ −)	7.66(+ −)	+0.23	0.64(− +)	9.00(+ −)	−0.07
+85° −95°	0.87(+ −)	8.19(+ −)	+0.11	1.01(− +)	9.30(+ −)	−0.11
+90° −90°	0.00	8.66(+ −)	0.00	1.41(− +)	9.60(+ −)	−0.15
+95° −85°	0.87(− +)	9.06(+ −)	−0.10	1.77(− +)	9.80(+ −)	−0.18
+100° −80°	1.74(− +)	9.40(+ −)	−0.18	2.13(− +)	9.93(+ −)	−0.21
+105° −75°	2.59(− +)	9.66(+ −)	−0.27	2.45(− +)	10.00(+ −)	−0.25
+110° −70°	3.42(− +)	9.85(+ −)	−0.35	2.79(− +)	9.98(+ −)	−0.28
+115° −65°	4.23(− +)	9.96(+ −)	−0.42	3.09(− +)	9.88(+ −)	−0.31
+120° −60°	5.00(− +)	10.00(+ −)	−0.50	3.36(− +)	9.70(+ −)	−0.35
+125° −55°	5.74(− +)	9.96(+ −)	−0.58	3.61(− +)	9.43(+ −)	−0.38
+130° −50°	6.43(− +)	9.85(+ −)	−0.65	3.84(− +)	9.10(+ −)	−0.42
+135° −45°	7.07(− +)	9.66(+ −)	−0.73	4.05(− +)	8.75(+ −)	−0.46
+140° −40°	7.66(− +)	9.40(+ −)	−0.82	4.20(− +)	8.30(+ −)	−0.51
+145° −35°	8.20(− +)	9.06(+ −)	−0.90	4.34(− +)	7.80(+ −)	−0.56
+150° −30°	8.66(− +)	8.66(+ −)	−1.00	4.45(− +)	7.20(+ −)	−0.62
+155° −25°	9.06(− +(	8.19(+ −)	−1.11	4.52(− +)	6.60(+ −)	−0.68
+160° −20°	9.40(− +)	7.66(+ −)	−1.23	4.55(− +)	5.88(+ −)	−0.77
+165° −15°	9.66(− +)	7.07(+ −)	−1.37	4.54(− +)	5.15(+ −)	−0.88
+170° −10°	9.85(− +)	6.43(+ −)	−1.53	4.51(− +)	4.38(+ −)	−1.03
+175° −5°	9.96(− +)	5.74(+ −)	−1.74	4.43(− +)	3.58(+ −)	−1.24

In each parentheses the first polarity corresponds to the RLF-plane direction listed in the first vertical column; the second, in the second vertical column.

The quotients may also be represented in curve form as shown in diagram B (Fig. 4). It includes quotients between +3 and −3, because most results are within this range. In this diagram the quotients are indicated at the two vertical borders. Each scale mark represents 0.04. At the two horizontal borders the conventional RLF plane directions are indicated in degrees. Each scale mark represents 2 degrees. The solid curves correlate directions and quotients that are valid for the

Burger triangle; the dashed curves correlate directions and quotients that are valid for the Einthoven triangle. This diagram may be used as follows: Note the polarity of e_1. If it is positive, use the bottom horizontal border; if it is negative, use the top one. Calculate the quotient e_1/e_3, and then correlate this value by means of proper curves to the direction in the Einthoven triangle and in the Burger triangle.

Example 2.—If the average normal ÂQRS is +58° obtained in the Einthoven triangle, to find its "true" direction in the Burger triangle, proceed as follows: The value +58° is indicated on the bottom horizontal border. The dashed curve correlates it to quotient +1.1. By means of the solid curve this quotient correlates on the bottom horizontal border to +32°, which is the "true" direction in the Burger triangle.

From this diagram it also becomes evident that, other factors being constant, the inaccuracy of the Einthoven triangle is dependent upon the "true" vectorial direction. It may be seen that directions obtained in the Einthoven triangle are more inaccurate when dashed and solid curves are more distant from each other, less inaccurate when they approach each other, and incidently accurate when the two curves intersect.

SUMMARY

The relationship between bipolar limb leads and cardiac vector in the RLF plane was considered in five sections.

1. Various Burger triangular shapes were correlated with the Einthoven triangle. Results indicated that the Einthoven triangle is inaccurate for subjects possessing Burger triangles of either scalene or isosceles shapes. As a rule, the more the Burger triangle departs from the equilateral, the more the vectorial direction, calculated in the Einthoven triangle, deviates from the true one.

2. Using the criteria given in the above section, a study was made of the influence of heart vector eccentricity and length in the inaccuracy of the Einthoven triangle by means of an electrolytic model. It was observed that the inaccuracy of the Einthoven triangle was affected more by the eccentricity than by the length of the "heart vector." Although the heart vector length also exercised an influence in this regard, the longer the vector (dipole length) the more inaccurate is the Einthoven triangle. Furthermore, the degree of inaccuracy of the Einthoven triangle, if other factors remain equal, depends not solely on the distance between the eccentric position and the geometric center, but on the position itself in the electrolytic model.

3. Burger triangles were constructed directly from living toad hearts in situ, using the graphic method described by Wilson and associates. Burger triangles from toads were similar under similar conditions to those that Wilson obtained from a current dipole located on the anterior aspect of the living human thorax. Depolarization and repolarization Burger triangles from the same toads were almost identical. This suggested that the hypothesis that QRS and T vectors from the same subjects differ in length and occupy different heart regions could not be confirmed by biologic experiments, at least not on toads.

4. In the fourth section a modified technique to construct a Burger triangle with coordinate scales was described. Such a triangle has some interesting features; namely, it obeys the Einthoven law, synthesizes the data of limb leads 1, 2, and 3 into a heart vector arrow within the triangle, or conversely, projects the heart vector arrow on the three sides of the triangle to yield bipolar limb lead data.

5. Described in detail in the final section were two diagrams (A and B) that yielded simultaneous results for the Einthoven triangle and the "average" Burger triangle. Diagrams may also be used to convert Einthoven data into Burger data. From diagram B it is easily seen that, other factors being equal, the inaccuracy of the Einthoven triangle depends upon vectorial direction itself. In other words, the directions obtained in the Einthoven triangle are more inaccurate when referred curves are more distant from each other, less inaccurate when they approach each other, and incidently accurate when they intersect.

I wish to express my sincere appreciation to those persons whose interest and efforts made this study possible: Dr. M. D. Santos, Dr. G. R. Herrmann, Dr. M. R. Hejtmancik, Mr. G. W. Newman, Miss J. S. Wolfer, and my wife Maria Hegemann.

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Case Reports

Spontaneous Rupture of the Pulmonary Artery in Pulmonary Hypertension

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INTRODUCTION

Spontaneous rupture of the pulmonary artery, a very rare event, has been defined in earlier literature as a break in the continuity of the vessel wall which occurs without evidence of previous trauma, aneurysm, or gross extrinsic pathologic changes. McNaught and Dock,[1] in 1935, reviewed this subject, reported one case, and found only two previous cases. Since their report we have found only five other cases which could be defined as spontaneous rupture of the pulmonary artery according to the above criteria. Most of the previously reported cases have been associated with congenital heart disease, especially patent ductus arteriosus, and rheumatic heart disease with mitral stenosis. The following two cases are of special interest because neither type of heart disease was present; at autopsy, the pulmonary arterial system was almost totally occluded by thrombi. To our knowledge, no such cases have been reported previously.

CASE REPORTS

CASE 1.—A 66-year-old married white woman was admitted to Colorado General Hospital for the last time on April 7, 1957, complaining of increasing dyspnea, hemoptysis, diarrhea, and extreme weakness of 2 weeks' duration. The admission diagnosis was pulmonary infarction.

This patient had had pulmonary tuberculosis in 1927, and had been chronically ill for many years thereafter. About 7 years prior to her death she developed congestive heart failure and was maintained on digitalis until her death. Four years prior to her death she was treated for pneumonia, and shortly afterward developed the classic findings of thrombophlebitis in her right leg. Because of recurrent episodes of pulmonary infarction following this (Fig. 1), the inferior vena cava was ligated in January, 1954. The chest roentgenogram made 1 year later showed the right pulmonary artery to be more dilated than previously. The clinical impression was pulmonary hypertension due to obstruction of blood flow. She was seen periodically for the next 2 years in the Cardiac and Peripheral Vascular Disease Clinics and was not readmitted to the hospital until her final admission on April 7, 1957.

Upon physical examination at the time of her final admission she appeared to be chronically

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ill, sitting upright in bed and in acute respiratory distress. The blood pressure was 140/100 mm. Hg, the pulse rate was 110 per minute and regular, and the respiratory rate was 50 per minute. The chest was resonant to percussion; the diaphragm did not descend with deep inspiration, and moist râles were heard at both bases. Examination of the heart revealed an apical thrust, and normal sinus rhythm with frequent premature contractions. No murmurs were heard; P_2 was louder than A_2. The edge of the liver was felt four fingerbreadths below the right costal margin and was very tender. There was 3+ ankle edema and marked cyanosis of the extremities.

Admission laboratory studies showed the following: hemoglobin, 17.5 Gm.; hematocrit, 53 per cent; leukocyte count, 6,450. Sputum culture showed a predominance of *Diplococcus pneumoniae*. Electrolyte studies were normal. Chest roentgenograms confirmed the previous finding of a prominent right pulmonary artery which terminated abruptly (Fig. 2). No new pulmonary lesions were seen. An electrocardiogram showed right ventricular hypertrophy and digitalis effect (Fig. 3).

Throughout the 2 days of her final hospital admission, the patient had severe paroxysms of coughing. On April 9, the day of death, she complained of sudden onset of severe left precordial pain which radiated to the left infrascapular region. The patient died suddenly within 6 hours after onset of the pain.

Autopsy Findings.—

Gross Examination: The body was that of a moderately obese white woman, 65 years of age, 165 cm. in length, and 116 pounds in weight. The pericardial space contained 370 Gm. of clotted blood and 50 ml. of fluid blood. The heart weighed 450 grams.

There was a 1-cm. fresh laceration on the ventral surface of the pulmonary artery 2 cm. distal to the pulmonic valve. The pulmonary artery was moderately dilated at the site of rupture, but this dilation was not thought to be an aneurysm. No atherosclerotic plaques were seen and the intima was smooth. There was no evidence of dissection of blood in the arterial wall.

Distal to the site of laceration, both pulmonary arteries were almost completely occluded by old, firm, red-gray, laminated, adherent thrombi which originated near the bifurcation. The right ventricle was moderately enlarged and thickened but no other abnormalities were found.

The lungs weighed 700 and 650 grams. There was moderate emphysema. The aorta was moderately atherosclerotic. The liver weighed 1,820 grams and showed chronic passive congestion, early portal cirrhosis, and slight fatty metamorphosis.

Microscopic examination: Sections of the pulmonary artery adjacent to the site of rupture showed an intact intima. There was slight fragmentation of connective tissue fibers immediately beneath the intima and the media, and a moderate increase in granular basophilic interstitial material. The nuclei of the connective tissue cells were small and widely scattered. There was fragmentation of connective tissue in the adventitia, with some focal linear infiltration of erythrocytes and neutrophiles (Fig. 4).

The arterioles in the lungs were thickened; some were obliterated by dense fibrous tissue, and others had recanalized. The alveolar septa were thickened and contained a large number of pigmented macrophages. The liver showed chronic passive congestion.

CASE 2.—A 60-year-old married white woman was admitted to St. Anthony's Hospital for the last time in July, 1958, complaining of left precordial pain with radiation into the left upper arm, of 1 day's duration. The admission diagnosis was myocardial infarction.

She had had intermittent allergic bronchial asthma since her teens but had responded well to ephedrine, epinephrine, and other medications until about 3 years prior to her death, when she developed more dyspnea and edema of her legs. She was then given digitalis regularly and mercurial diuretics periodically. About 7 months prior to her final admission, she was hospitalized for 8 days because of an increase in her cough and dyspnea, associated with a respiratory infection. Treatment with antibiotics, oxygen, and bronchodilators was quite effective, and she then got along well for about 3 months.

Physical examination at the time of her final hospital admission revealed a blood pressure of 120/84 mm. Hg, a regular pulse at a rate of 80 per minute, and a respiratory rate of 20 per minute. She was a somewhat cyanotic, small, chronically ill-appearing woman who was coughing. Moist râles were heard at both lung bases posteriorly; medium to coarse râles and rhonchi were audible throughout the lung fields. The heart was enlarged to the left; no murmurs were heard. The abdomen was protuberant; shifting dullness was present. Moderate pretibial edema was found.

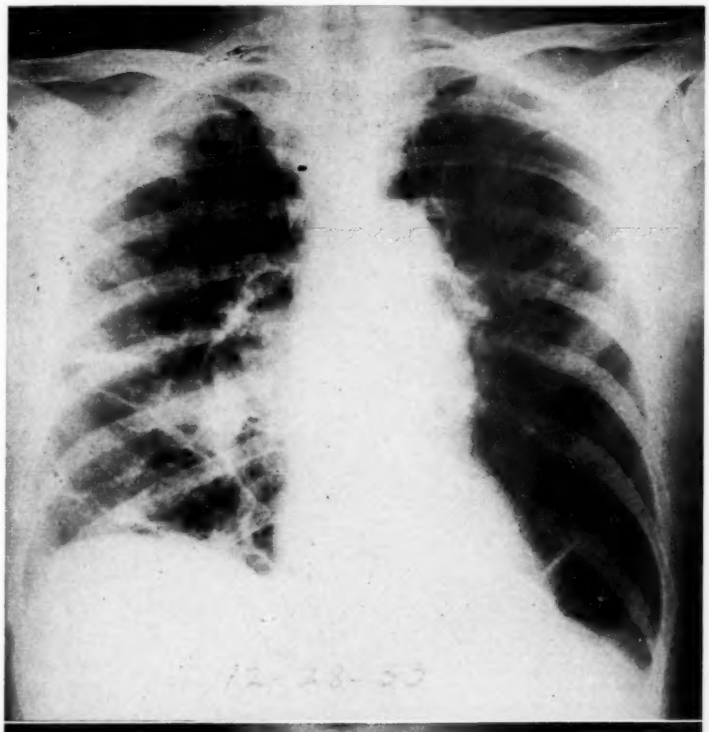

Fig. 1.

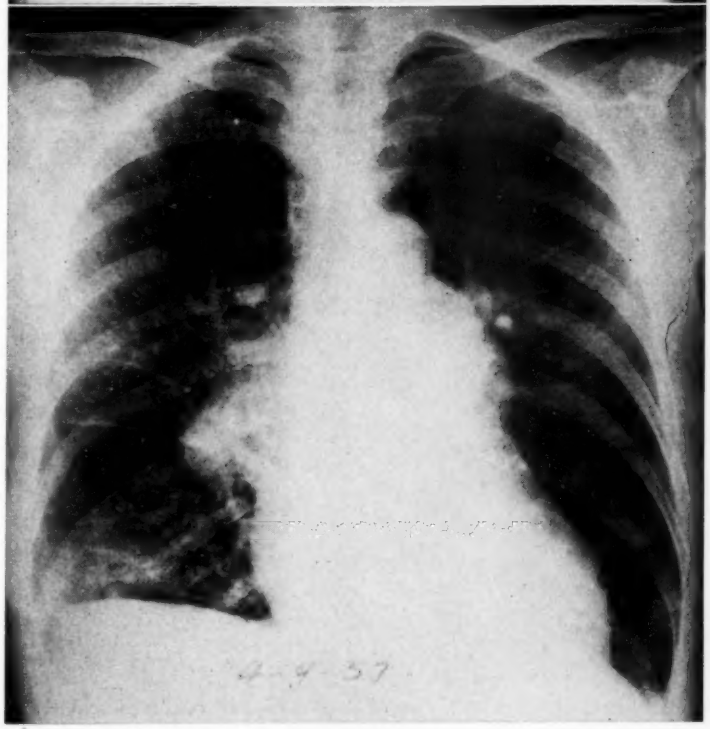

Fig. 2.

Fig. 1.—Case 1. Posteroanterior roentgenogram of the chest, showing a resolving pulmonary infarction in the right middle lobe.

Fig. 2.—Case 1. Posteroanterior roentgenogram of the chest, showing an increase in size of the cardiac silhouette and increased prominence of the pulmonary arteries. The right pulmonary artery terminates abruptly.

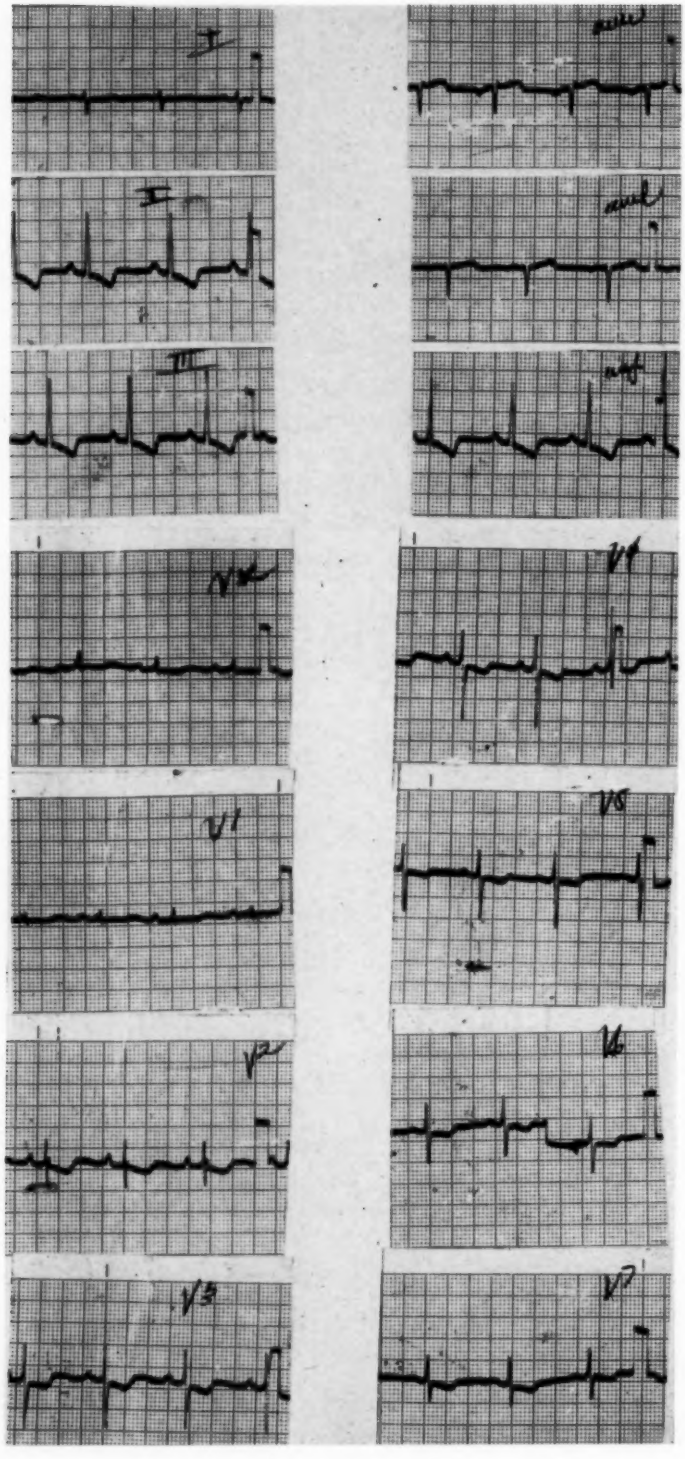

Fig. 3.—Case 1. Electrocardiogram interpreted as showing right ventricular hypertrophy and digitalis effect.

Admission laboratory work revealed a hematocrit of 68 per cent and leukocyte count of 9,850. Chest x-rays from her previous admission showed cardiac enlargement, primarily right ventricular, with marked prominence of the pulmonary arteries. Comparison with films taken 3 years previously showed an increase in cardiac size and pulmonary vascular markings (Figs. 5 and 6). Electrocardiograms showed right ventricular and right auricular hypertrophy (Fig. 7).

Serial electrocardiograms showed no acute changes. The precordial pain subsided after a few injections of Demerol. On the fourth day after admission, after 3 uneventful days, she had severe paroxysms of coughing and was quite dyspneic. She died that evening a few minutes after the nurse found her gasping for breath and very cyanotic.

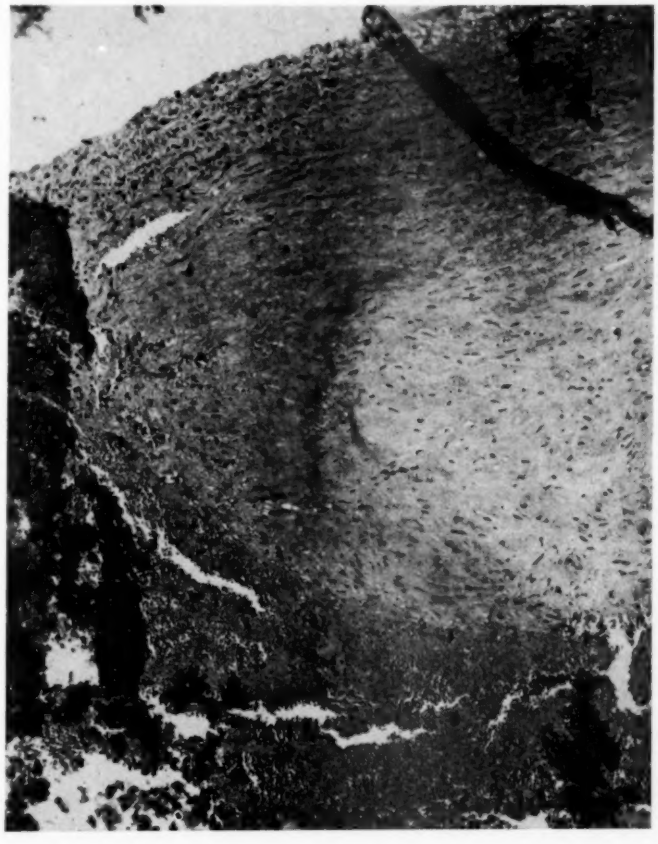

Fig. 4.—Case 1. Section of the main pulmonary artery at the site of rupture. (See autopsy findings.)

Autopsy Findings.—

Gross Examination: The body was that of a fairly well-developed, well-nourished, white woman, 60 years of age, 150 cm. in length, 115 pounds in weight. The pericardial space contained 250 ml. of partly clotted and fluid blood. There was a longitudinal laceration 4 cm. in length along the left lateroanterior surface of the pulmonary artery, which began 1 cm. distal to the pulmonic valve (Fig. 8). The right ventricle was severely hypertrophied, measuring 1.2 cm. in thickness, as compared with the left ventricle, which measured 1.8 cm. The heart was otherwise normal.

The pulmonary artery, which was estimated to be twice the normal caliber, was thin walled and dilated distal to the pulmonic valve. There was a laminated, well-organized, striated thrombus which began 5 cm. above the pulmonic valve and nearly occluded both branches of the pulmonary artery. There was focal, waxy roughening of the pulmonary arterial intima throughout; however, no definite atheromatous plaques were seen near the site of rupture.

Fig. 5.

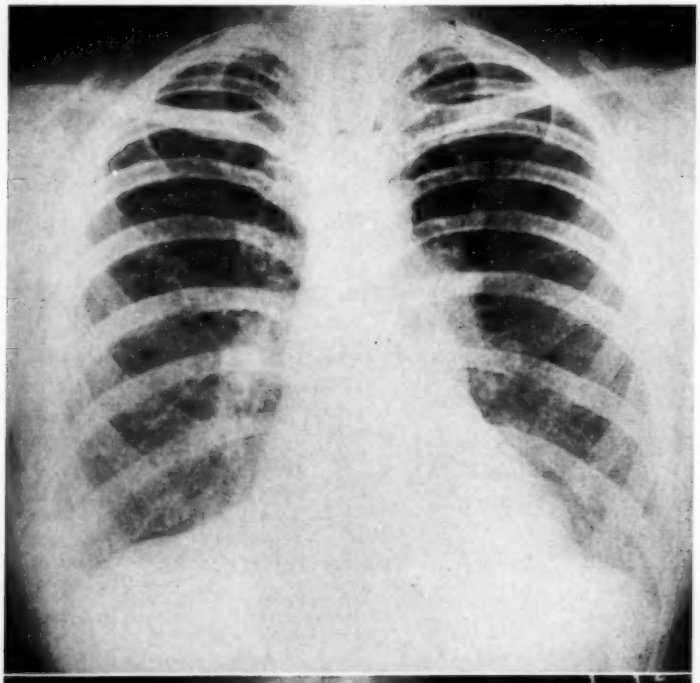

Fig. 6.

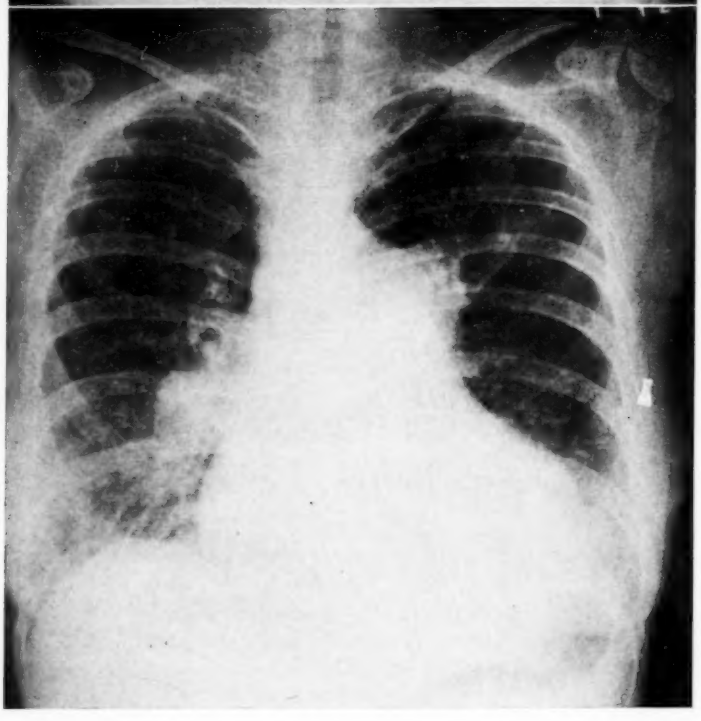

Fig. 5.—Case 2. Posteroanterior roentgenogram of the chest taken 4 years prior to the patient's death.

Fig. 6.—Case 2. Posteroanterior roentgenogram of the chest taken 6 months prior to the patient's death, showing marked increase in cardiac size and prominence of the pulmonary arteries. The cardiac enlargement is primarily right ventricular.

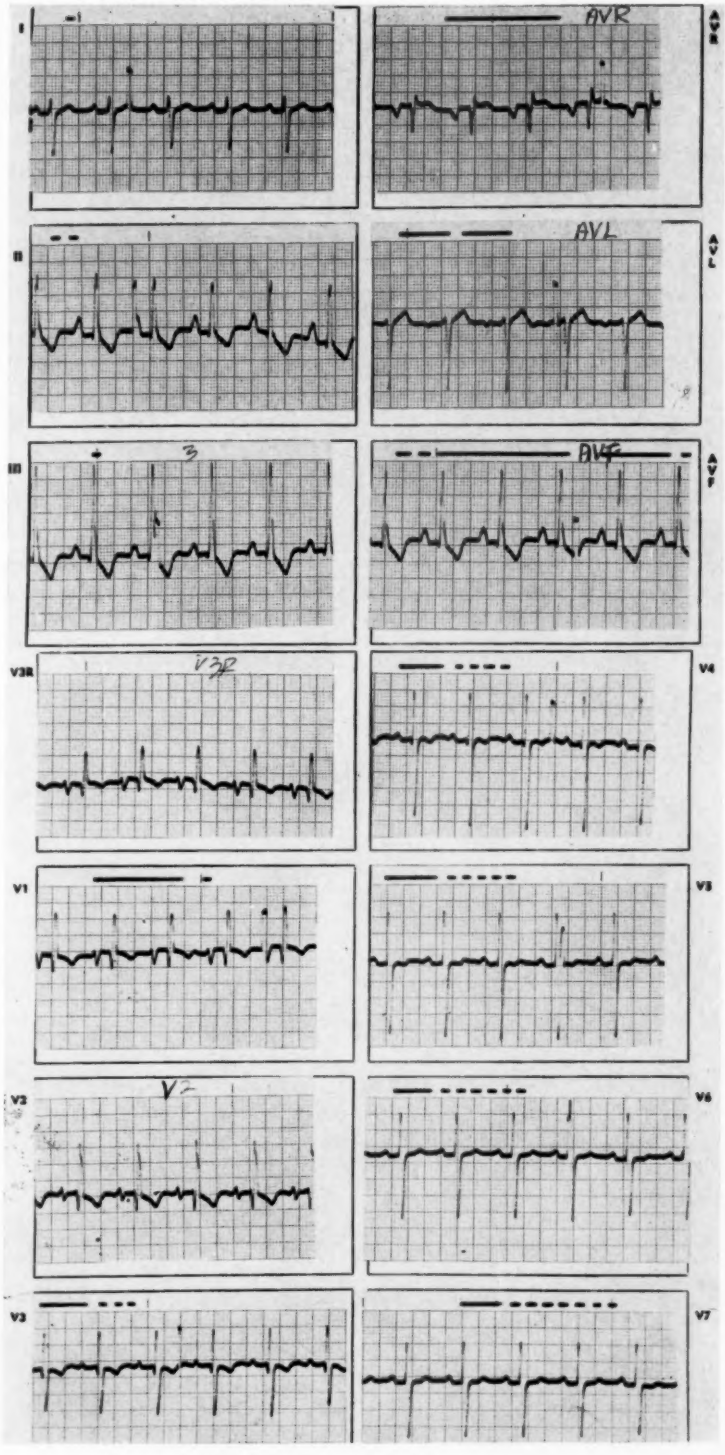

Fig. 7.—Case 2. Electrocardiogram taken 3 days prior to the patient's death, interpreted as showing right ventricular and right auricular hypertrophy.

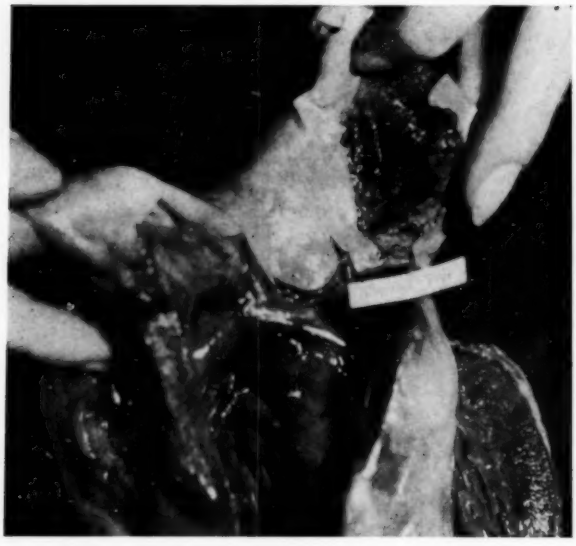

Fig. 8.—Case 2. Gross specimen of the heart showing the longitudinal laceration in the main pulmonary artery beginning 1 cm. distal to the pulmonic valve.

Fig. 9.—Case 2. Section of the main pulmonary artery at the site of rupture. (See autopsy findings.)

Microscopic Examination: Sections of the pulmonary artery from the area of rupture showed a slightly convoluted intima with very slight granulation (Fig. 9). There was some separation of fibers and a moderate amount of basophilic interstitial material in the media. The vasa vasorum were unremarkable. The adventitia showed some slight dissection of interstitial planes by erythrocytes and hyaline material, suggesting early thrombosis.

Examination of multiple sections of lung showed moderate to moderately severe thickening of the smaller pulmonary arteries and arterioles. There was slight to moderate septal fibrosis, with evidence of focal atelectasis, emphysema, and acute and chronic congestion.

DISCUSSION OF CASES

Severe pulmonary hypertension was undoubtedly present in both of our cases, since almost total occlusion of the pulmonary arterial circulation was found in both instances. In Case 1 the pulmonary hypertension probably resulted from progressive obstruction of the pulmonary arterial circulation secondary to embolism and thrombosis. In Case 2, cor pulmonale from long-standing bronchial asthma had been present for some time, and the pulmonary arterial thrombi probably formed secondarily.

Rupture of the pulmonary artery followed severe paroxysms of coughing in both cases. The Valsalva maneuver is known to increase pulmonary arterial pressure. McCann[11] demonstrated this during cardiac catheterization studies of two patients with tussive syncope. Sharpey-Schafer[12] demonstrated that intermittent coughing caused rapid intrathoracic pressure transients up to greater than 300 mm. Hg, and that these were also transmitted to peripheral arteries, veins without valves, and the chambers of the right side of the heart. The circulatory and intrathoracic changes in pressure after coughing were proportional to the violence of the cough. Rupture of weakened vessels in a wide variety of sites has been reported following Valsalva maneuvers. Rupture of the pulmonary artery has occurred during defecation.[9] In our two cases, it appears that the Valsalva maneuver induced by coughing, in addition to the pre-existing pulmonary hypertension and obstruction to outflow of the pulmonary artery, might well have produced an extremely high pressure within the pulmonary artery proximal to the point of obstruction; rupture then ensued.

DISCUSSION OF PATHOLOGY

We attempted to determine in our cases whether there was a pulmonary arterial lesion of sufficient severity to explain a rupture. Brenner[13] states that "sclerosis of the vessels of the pulmonary circulation is almost constantly found at autopsy." Steinberg, quoted by Brenner, reports an incidence of sclerosis of the pulmonary artery in up to 65 per cent of 500 unselected autopsies. Wartman[14] found varying degrees of sclerosis of the pulmonary artery in approximately 50 per cent of autopsies on patients who were 60 years of age or older. The changes usually seen histologically in sclerotic pulmonary arteries consist of subintimal thickening, increased connective tissue in the media, moderate and scattered mononuclear leukocytic infiltration in the adventitia, and thickening of the walls of the vasa vasorum.

TABLE I. PREVIOUS REPORTS OF RUPTURE OF THE PULMONARY ARTERY

AUTHOR AND DATE	NO. OF CASES	AGE, SEX	UNDERLYING CARDIOVASCULAR DISEASE	SPONTANEOUS RUPTURE	PATHOLOGY OF THE PULMONARY ARTERY	REMARKS
Moench,[2] 1924	1	29, F	Congenital (P.D.A.)	No	No microscopic studies reported	Rupture of aneurysm of the pulmonary artery
Favorite,[3] 1934	1	18, M	Congenital	Yes	Separation and fragmentation of elastic fibers of the media	Pulmonary artery dilated but no aneurysm. Several rupture sites. Rupture followed 1 week of coughing
McNaught and Dock,[1] 1935	1	44, F	Rheumatic (mitral stenosis)	Yes	Degenerative changes of media and adventitia	Authors felt that medial degeneration plus pulmonary hypertension caused rupture
Longland,[4] 1943	1	68, M	None	Yes	No degenerative changes present	Three separate tears in the pulmonary artery —only one was complete through all layers
Lindert and Correll,[5] 1950	1	67, F	Congenital (P.D.A.)	No	No microscopic studies reported	Rupture of aneurysm of the pulmonary artery
Ohela and Teir,[6] 1954	3	61, M 72, F 31, M	None None Congenital (P.D.A.)	(?)	Cases 1, 2: media thickened, derangement of medial fibers, blood in interfibrous spaces. Case 3: medial degeneration	These cases from a review of 2,960 autopsies. Dissecting aneurysm in 2 cases. Trauma could have caused rupture in the third
Thomas et al.,[7] 1955	1	42, F	Rheumatic (mitral stenosis)	Yes	Fragmentation of elastic fibers and medial degeneration	Authors felt that medial degeneration plus pulmonary hypertension caused rupture
Madeloff and Rushton,[8] 1956	1	56, F	Rheumatic (mitral stenosis)	Yes	No medial degeneration. Rupture site involved an atheromatous plaque	
Kodolova,[9] 1956	1	40, M	Rheumatic (mitral stenosis)	Yes	Medial degeneration with some fragmentation of elastic fibers	Extensive pulmonary artery thromboses. Died suddenly during defecation
Condry and Nefflin,[10] 1958	1	61, M	None	Yes	Medial degenerative changes. Rupture site involved an atheromatous plaque	Authors felt that rupture was due to primary arteriosclerosis of pulmonary artery

In our cases, although sclerosis and thrombosis of the pulmonary artery were present, these processes were not seen at the site of rupture. There was moderate dilatation and thinning of the wall consistent with the probable elevation of pressure in the proximal pulmonary artery; this dilatation was thought to be less than "aneurysmal."

Since at least 1935, it has been thought that the pulmonary artery may be affected by medial necrosis, the same basic process which occurs in dissecting aneurysm of the aorta. However, pictures and descriptions supplied in some of the reports proposing this origin of rupture of the pulmonary artery would seem almost to fall within the limits of normality, including those changes due to the aging process and the prevalent sclerosis described above. The normal pulmonary artery may have scanty and widely scattered elastic laminae, abundant connective tissue, short-branching irregular elastic fibers, and large plates of dense, practically acellular tissue consisting of fine fibrils in a homogeneous pale matrix. The irregularities of the arrangement of medial fibers are increased and connective tissue is increased in large amount in the course of the aging process. Our cases had histologic changes consistent with the usual aging processes.

SUMMARY

Two cases of spontaneous rupture of the pulmonary artery are reported. A review of the literature since McNaught and Dock's review of this subject in 1935, revealed only five well-documented cases of spontaneous rupture according to the criteria mentioned. None of the previous cases showed solely extensive thrombosis of the pulmonary artery without congenital or rheumatic heart lesions. The area of rupture is nearly always immediately distal to the pulmonic valve and usually extends longitudinally for several centimeters. Because of this location, practically every case is associated with hemopericardium. A constantly demonstrable etiological lesion has not as yet been found. In our cases the pulmonary artery at the site of rupture was free of significant degenerative change in excess of that described as being due to aging.

It is not known why this condition is so rare, since the combination of pulmonary vascular degenerative changes and pulmonary hypertension is fairly common.

ADDENDUM

Since the preparation of this manuscript, the following case of rupture of a large aneurysm of the main pulmonary artery associated with severe pulmonary hypertension has been called to our attention by Dr. Abe Ravin, who has kindly given us permission to include the case in this report.

Report of a Case.—A 27-year-old white man with a long-standing history of dyspnea, fatigue, and cyanosis, was thoroughly studied in 1948 and 1949. Initial cardiovascular symptoms appeared at about age 7. A diagnosis of rheumatic valvulitis was made, but no subsequent typical episode of rheumatic fever occurred. He had been aware of some cyanosis of his fingernails and lips for years. During the few years prior to his evaluation he was aware of increasing dyspnea on very mild exertion and a dull precordial pain which was not typical of angina pectoris. Several phlebotomies for moderately severe polycythemia produced only slight relief of symptoms.

Physical examination in 1948, revealed a blood pressure of 120/80 mm. Hg, and a regular pulse of 100 per minute. He appeared chronically ill, with some dyspnea at rest. There was marked clubbing of the fingers; the lips and nails were moderately cyanotic. The lung fields were clear. The heart was enlarged to the left, 10 cm. from the mid-sternal line in the fifth intercostal space. A faint thrill was felt over the pulmonic area. The only murmur heard was a short, harsh, systolic murmur, which was loudest over the pulmonic area. The second sound over the upper left sternal border was markedly accentuated.

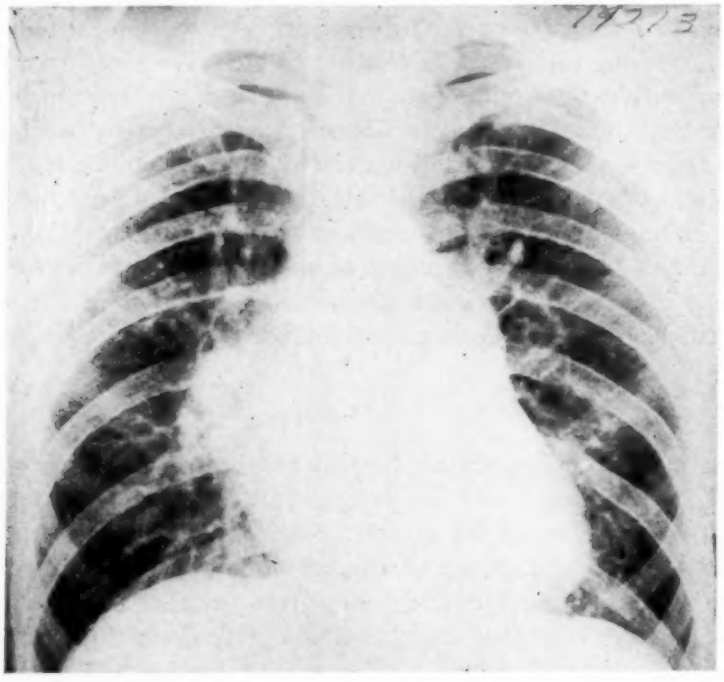

Fig. 10—Case reported in the Addendum. Posteroanterior reoentgenogram of the chest, showing cardiac enlargement, predominantly right ventricular, and prominence of the pulmonary arteries.

Roentgenographic studies revealed cardiac enlargement, predominantly right ventricular, and a pulmonary artery with evidence of pulmonary hypertension and increased pulsation of the pulmonary arteries (Fig. 10). The electrocardiogram showed marked right ventricular hypertrophy. The hematocrit was 66 per cent. Cardiac catheterization revealed a systemic arterial desaturation of 88 volumes per cent and a venous oxygen saturation of 68 volumes per cent. Pressures in the right ventricle and right pulmonary artery were similar and markedly elevated: 112/55 mm. Hg in the pulmonary artery, and 115/10 mm. Hg in the right ventricle. The right ventricular pressure was equal to the systemic arterial pressure. A diagnosis of ventricular septal defect with marked pulmonary hypertension and right-to-left shunt (Eisenmenger's syndrome) was considered.

The patient died a few years after this evaluation; the heart and lungs were sent to Denver for pathologic study.

Autopsy Report.—

Gross Examination: The specimen consisted of the heart, great vessels, and both lungs. The heart was greatly enlarged, weighing 470 grams. The left ventricle was 20 mm. in thickness, and the right ventricle was 17 mm. The valves were thin and competent and no congenital anomalies were described. There was a gigantic aneurysm involving the entire length of the main trunk of the pulmonary artery and extending into the proximal 9 cm. of the right, and 7 cm. of the left, main branches. The main aneurysm measured 16 by 13 by 11 cm. and was filled by a large throm-

bus of approximately the same dimensions as the aneurysm (Fig. 11). The outer portion of the thrombus was partly calcified and was adherent to the wall of the pulmonary artery. The anteromedial wall of the main trunk of the pulmonary artery showed an oblique linear rupture 2.5 cm. in length and located about 5 cm. above the pulmonic valve. No abnormalities of the lungs were found.

Microscopic examination: The portions of the pulmonary artery which showed pathologic changes had hyaline sclerotic thickening of the intima which frequently blended imperceptibly with the thrombus. The media was thinned in many areas. Elastic-fiber stains demonstrated a moth-eaten appearance due to the presence of numerous areas of destruction of elastic fibers. The elastic fibers had disappeared completely in certain areas, and there was a homogeneous appearance of the media. Sections taken from the vicinity of the rupture showed complete necrosis, with presence of scattered hyperchromatic nuclear fragments. The adventitia showed a conspicuous lymphocytic infiltration, sometimes located around vasa vasorum. Sections of the lungs were normal.

Fig. 11.—Case reported in the Addendum. Gross specimen of the heart, showing a gigantic aneurysm of the main and right and left branches of the pulmonary artery. The aneurysm was filled by a large thrombus, fragments of which are shown at the left.

Discussion.—Although this case is not one of spontaneous rupture of the pulmonary artery, because of the presence of a large aneurysm of the pulmonary artery, it was associated with severe pulmonary hypertension and there was no evidence of congenital or rheumatic heart disease. In this latter respect, it was similar to our two cases. Also, as in our cases, the pulmonary artery distal to the point of rupture was almost totally occluded by a large thrombus. Severe degenerative changes of the media of the pulmonary artery were present in this case, whereas in our two cases such changes were not observed. This case probably represents severe idiopathic pulmonary hypertension terminating in rupture of a large aneurysm of the main pulmonary artery.

We wish to express our appreciation to Dr. Charles T. Brierty and the Department of Pathology of the University of Colorado Medical Center for the use of the pathology material in Case 1. We also wish to express our appreciation to Drs. Abe Ravin and Karl T. Neubuerger, Denver, Colo., for the use of the case presented in the Addendum. Finally, we wish to acknowledge the assistance of the late Dr. James B. McNaught, of the University of Colorado Medical Center.

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Progressive Muscular Dystrophy With 1:1 Atrial Flutter

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INTRODUCTION

Progressive muscular dystrophy, while not being exactly rare, is not a common disease, whereas 1:1 atrial flutter is extremely rare and, to our knowledge, has not been reported in association with progressive muscular dystrophy. We believe, therefore, that the following report of a case of progressive muscular dystrophy with 1:1 atrial flutter may be of interest.

CASE REPORT

This 39-year-old white man was admitted to the hospital in August, 1957, in a state of shock. The skin was clammy and covered with a profuse, cold perspiration. The blood pressure was unobtainable, and the radial pulses could not be felt. The lungs were clear to auscultation and percussion. Cardiac auscultation revealed tachycardia and very distant heart sounds. An electrocardiogram showed a ventricular rate of 280 and was interpreted as indicating atrial flutter with 1:1 A-V conduction (Fig. 1). The liver, spleen, and kidneys were not felt.

The patient was immediately digitalized and given Levophed, with the resultant slowing of the ventricular rate to an average of 72 beats per minute. An electrocardiogram taken at this time showed an atrial flutter, with mainly a 4:1 block, occasionally a 2:1 block (Fig. 2).

The patient had been admitted many times to different hospitals, the first time being in 1947, when he was admitted because of pain in the chest, shortness of breath, and muscular weakness. Numerous electrocardiograms taken during the past 10 years showed 1:4, occasionally 1:2, atrial flutter. He had taken digitalis at different times in the past, but had had none during recent months. In the past, several attempts had been made with quinidine to convert the atrial flutter to a regular sinus rhythm, but were unsuccessful. Approximately 20 years ago, when he was 20 years of age, he began to complain about weakness of the upper and lower extremities. He developed a foot drop about 10 years ago. He denied ever having had rheumatic fever. The patient completed the ninth grade, failed in the first, fourth, fifth, and seventh grades.

The family history was noncontributory. There was no history of muscular dystrophy in his family.

After the patient had recovered from his acute episode and returned to his usual status, the additional physical examination revealed a fairly well-nourished and well-developed, but mentally sluggish, white man of the stated age. The facies was rather dull and listless. The heart was enlarged to the left. There were no murmurs present. The blood pressure varied from 115/80 to 100/70 mm. Hg. The lungs were clear to auscultation and percussion. The abdomen was relaxed. The liver and the spleen were not felt.

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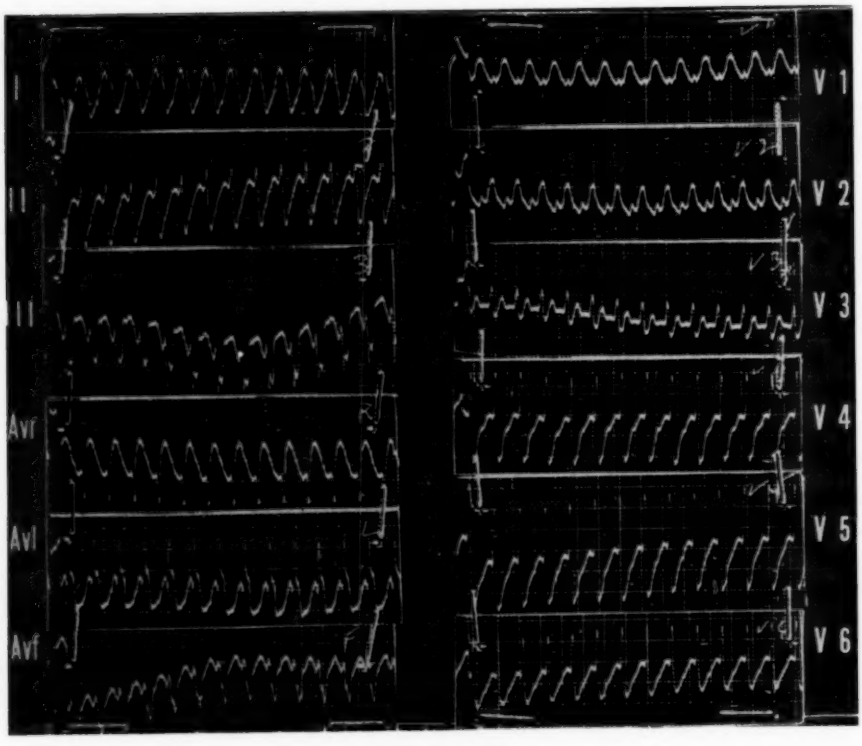

Fig. 1.—See text.

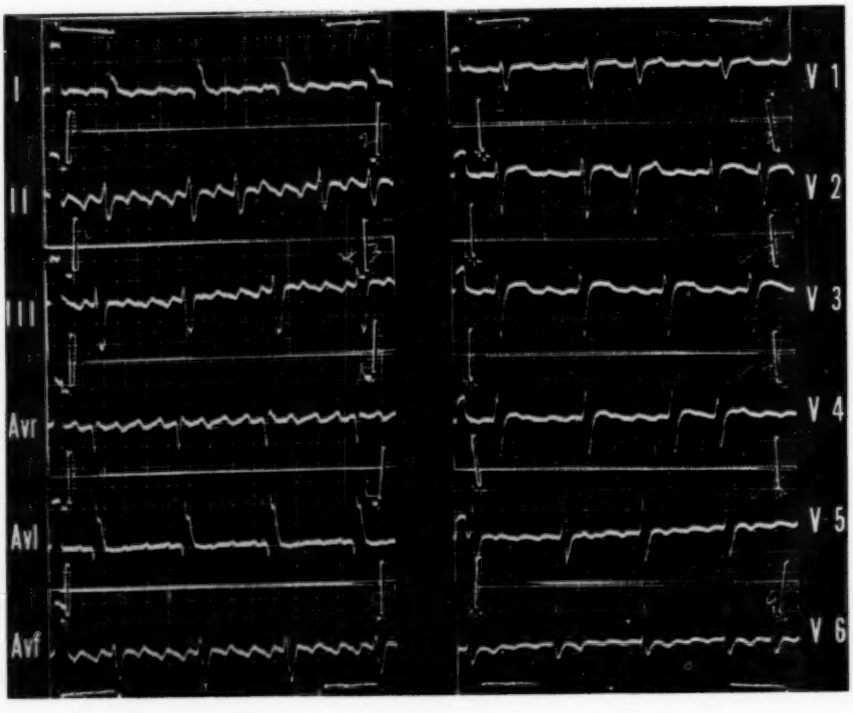

Fig. 2.—See text.

The x-ray films of the chest, taken in the anteroposterior and right and left anterior oblique views, showed enlargement of the left ventricle but no enlargement of the left atrium or of the right heart chambers.

The cranial nerves were normal. Motor power was decreased in all extremities. There was subjective numbness of fingers and toes; there was response to pinprick and to vibration. The biceps, triceps, ulnar, patellar, and Achilles reflexes were depressed to absent. The abdominal and cremasteric reflexes were present. No pathologic reflexes were elicited. There was atrophy of the musculature of the upper extremities and, to a lesser extent, of the lower extremities. There was no sensory involvement, no nystagmus or fibrillation. The speech was normal. The posture was stooped; the gait was slow and bordered on a steppage type.

Electromyographic studies were performed. The minimal activity record of the left quadriceps showed increased frequency of motor-unit firing of potentials of brief duration; the maximal activity record showed some increase in the frequency of motor-unit firing, with very little augmentation of the voltage. The brief duration of each potential, the increased frequency of motor-unit firing, and the low voltage developed on maximal contraction suggested myopathic origin of the electrical pattern, consistent with a diagnosis of muscular dystrophy.

Histologic examination of a biopsied skeletal muscle showed fatty infiltration, distortion, and alteration of the muscle fibers. There was considerable variation in the size of the individual fibers and, in some zones, fibrosis and proliferation of the sarcolemmic nuclei. Small vessels included in the section were not remarkable and did not attract attention. The findings were diagnosed as being consistent with muscular dystrophy (Fig. 3).

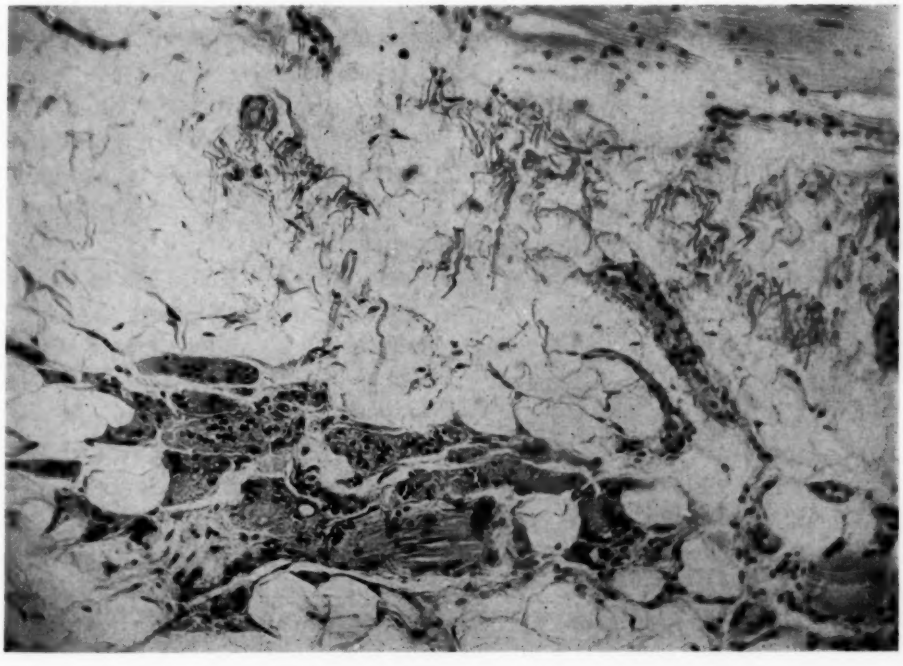

Fig. 3.—See text.

Laboratory Findings.—Routine urinalysis and hematograms were within normal limits. There was no eosinophilia. The sedimentation rate was 2, 6, and 8, respectively, on three occasions. Serology was negative. Spinal fluid was negative. Congo red test was negative. Myasthenia gravis was ruled out by the Prostigmin test.

Total protein, albumin-globulin ratio, blood chemistry, calcium, phosphorus, alkaline phosphatase, and electrolytes were all within normal limits. The radioactive iodine uptake was 17 per cent. The protein bound iodine was 4.66 mcg. per cent. The cholesterol was 200 mg. per

cent with 55 per cent esters. The bone marrow was normal. The total 24-hour urinary excretion of creatine on 3 different days was 276, 205, and 177 mg., whereas the 24-hour excretion of creatinine on the same days was 950, 1,015, and 965 mg.

Course in Hospital.—It was possible to convert the atrial flutter to a regular sinus rhythm. The patient was kept on maintenance doses of digitalis and quinidine.

DISCUSSION

Although not rare, progressive muscular dystrophy is not a common disease. It was first described clinically by Meryon,[1] in 1852. In 1931, Hough[2] roughly estimated the incidence of progressive muscular dystrophy to be approximately 6 per 100,000 population. Meerwein[3] collected 480 cases of progressive muscular dystrophy published before 1904. In 89 of these there was some abnormality of the heart or pulse. Nothacker and Netsky,[4] in reviewing 8,843 consecutive necropsies, from 1911 through 1949, found that there were 11 cases of progressive muscular dystrophy, and in 6 of those cases there were myocardial lesions. A survey of the literature by Storstein and Austarheim[5] showed that by the end of 1951, only 30 cases of progressive muscular dystrophy of the heart, with autopsy reports, had been published.

It has been estimated that the heart is involved in about 50 per cent of the cases of progressive muscular dystrophy, particularly that of the so-called "childhood type." Therefore, muscular dystrophy should be considered more frequently in the differential diagnosis of the more obscure forms of heart disease, such as "idiopathic myocarditis, idiopathic ventricular hypertrophy," especially in the absence of other etiology, such as rheumatic, hypertensive, arteriosclerotic, or congenital heart disease. The term "dystrophic heart disease" has been suggested for this entity by Berenbaum[6] and others.

Progressive muscular dystrophy can essentially be divided into two types: (1) the pseudohypertrophic form of childhood (Duchenne) and (2) the facioscapulohumeral type, having its onset at puberty (Landouzy and Dejerine). There is probably also a mixed type.

The laboratory findings reveal a diminished urinary excretion of creatinine and increased urinary excretion of creatine. There is also usually a diminished level of potassium and creatine in the muscles. Hypoglycemia is found in many cases, and sudden death is frequent in this condition. Pathologic findings in the heart usually show changes identical with those in the skeletal muscles, namely, areas of scarring which tend to divide the muscle fibers into individual fasciculi.[7] The entrapped muscle fibers undergo various changes: vacuolation, fragmentation, hypertrophy, shrinkage, and phagocytosis. The fat content of the scars is variable. The valves, the coronary arteries, and the epicardium are usually normal. According to Paul Wood,[8] there seems to be little relationship between the degree and severity of the skeletal myopathy and the cardiac involvement.

Clinically, as far as the cardiac involvement is concerned, these patients can be divided into three categories: (1) patients without clinical manifestations, (2) patients with congestive heart failure, and (3) patients with arrhythmias or tachycardias.

Patients with cardiac involvement may be perfectly well, then suddenly feel sick and experience palpitation, and break out in a cold sweat; not infrequently there may be a sudden shock-like state.[9] A soft systolic murmur at the apex has been found in a few instances. Intermittent gallop rhythm has also been present occasionally.

Electrocardiographic changes consisting of changes in the P wave and P-R interval, lengthening of the Q-T interval, and bundle branch block have been reported by all authors.[10-12]

To our knowledge, no case of muscular dystrophy with atrial flutter has been reported.

There is no definite proof that the cardiac involvement in our patient was due to muscular dystrophy, since no histologic examination of the heart muscle itself has been made. However, all other diagnostic possibilities, including subendocardial fibroelastosis, are unlikely. The long duration of the disease is not indicative of subendocardial fibroelastosis. To our knowledge, only one case of subendocardial fibroelastosis has been reported[13]—in an adult who died at the age of 71 with a history of anginal attacks of 15 years' duration. In our case the duration has been at least that long, and there is no history of anginal attacks. Likewise, our patient did not have emboli from mural thrombi, associated mitral, tricuspid, or aortic stenosis, or constrictive pericarditis, which have been described as suggestive of subendocardial fibroelastosis.[14,15] Finally, it is more logical to ascribe the condition of the patient to one disease entity rather than to two different disease entities. A presumptive diagnosis of cardiac involvement in cases of proved muscular dystrophy, without benefit of histologic examination of the heart muscle, has been made by other authors.[6,16]

Atrial Flutter With 1:1 A-V Conduction.—Atrial flutter with 1:1 A-V conduction is extremely rare. The first documented case was reported by Lewis,[17] in 1915. In 1956, Finkelstein and associates[18] reported 40 additional cases which had been described in the literature and added 6 cases of their own. In December, 1957, Marks[19] stated that 47 cases of atrial flutter with 1:1 A-V conduction had been reported in the world literature and added 1 case of his own. This illustrates the rarity of this condition. It is usually due to a serious organic condition like rheumatic, hypertensive, arteriosclerotic, and thyrotoxic heart disease. However, a few cases, with autopsy findings, without underlying organic heart disease have been reported.[18]

It is often difficult to make with certainty an electrocardiographic diagnosis of 1:1 atrial flutter because this condition can mask supraventricular paroxysmal tachycardia. Ventricular paroxysmal tachycardia has usually a ventricular rate of from 130 to 180 per minute; carotid sinus pressure is ineffective in lowering the rate and there is a slight irregularity of the R-R complexes, the atrial beat being at a slower rate and independent of the ventricles. This can be shown by esophageal leads in which the P waves are more prominent.[20] Finally, the QRS complexes are widened, slurred, notched, and bizarre. The electrocardiographic differential diagnosis between paroxysmal atrial tachycardia and 1:1 atrial flutter is more difficult. The mechanism during the attack in both conditions is the same, namely, an ectopic focus in the atrium, which is conducted

to the ventricles. (According to Prinzmetal,[21] paroxysmal atrial tachycardia, atrial flutter, and atrial fibrillation are different stages of basically the same process.) There are a few points to be made in favor of an atrial flutter rather than a paroxysmal atrial tachycardia: (1) A rate of 280 beats per minute is too fast for atrial paroxysmal tachycardia, except in infants. (2) If a patient has always had a clear-cut atrial flutter and then exhibits a tachycardia, which after the administration of digitalis returns again to flutter with a higher A-V block, it is more logical to assume that the attack is also one of atrial flutter. (3) Atrial paroxysmal tachycardia responds to carotid sinus pressure or digitalis, with a return to a normal sinus rhythm and not to a flutter, whereas in flutter a higher degree of A-V block will be obtained after carotid sinus stimulation or digitalis.

Because it produces irreversible changes if of long duration, 1:1 atrial flutter is a serious condition, necessitating immediate treatment. Finkelstein and associates[18] reported a case of a 16-year-old girl, without clinically demonstrable heart disease, who died as a result of congestive failure due to 1:1 flutter of 5 days' duration. Even autopsy showed only congestive heart failure.

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Restoration of Normal Conduction Following the Administration of Digitalis in a Case of WPW Syndrome

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Since 1930, when Wolff-Parkinson-White[1] first described the pre-excitation syndrome, many theories have been advanced in order to explain the abnormal mechanism. Experimental and pathologic evidence seems to support the hypothesis which was first advanced by Holzmann and Scherf[2] and Wolferth and Wood,[3] namely, the presence of an accessory pathway connecting the auricles with the ventricles, bypassing the A-V node.

The effect of drugs on this syndrome has been studied by different investigators, with varying results. It has been shown by Roberts and Abramson[4] and others[5-8] that quinidine has a pronounced affinity for the aberrant mechanism and depresses it, so that normal transmission of the sinus impulse takes place through the A-V node, producing a normal electrocardiogram. On the other hand, any substance with a greater affinity for the A-V node will depress it and allow propagation of the sinus impulse through the aberrant mechanism, with resulting abnormal electrocardiographic pattern.

Opinions concerning the action of digitalis on the WPW syndrome are in conflict. Most of the investigators believe that digitalis, by suppressing the A-V node, facilitates the appearance of the anomalous conduction, or if the latter is already present, perpetuates its continuance.

The present report deals with a case of WPW syndrome in which the administration of digitalis suppressed the abnormal conduction and restored a normal mechanism.

REPORT OF CLINICAL EXPERIMENT

Clinical Data.—The patient (P. B.) was a 42-year-old Negro man, who was admitted to Metropolitan Hospital on May 19, 1958, because of nonspecific pains in the joints. He stated that for the past year or so he had had intermittent pain in the interphalangeal joints, wrists, and ankles. He denied swelling, tenderness, or redness of the joints, and he had no fever. Twenty years ago he was treated for syphilis. He had no known history of cardiac disease and no symptoms referable to the cardiovascular system.

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Physical Examination.—The blood pressure was 137/80 mm. Hg, pulse was 75, and temperature and respirations were within normal limits. There was no venous distention.

Heart: The point of maximal impulse was in the sixth intercostal space in the anterior axillary line, with a left ventricular heave. A thrill was palpated over the aortic area. A loud, rough systolic murmur was heard all over the precordium and was transmitted to the neck. A diastolic blow was heard over the second right intercostal space and along the left sternal border. The second aortic sound was markedly diminished.

Abdomen: The liver and spleen could not be palpated.

Extremities: There was no apparent swelling or tenderness of the joints and no peripheral edema.

Laboratory Data.—Urine and blood counts were within normal limits. The erythrocyte sedimentation rate was 65; ASOT, 50; sheep cell agglutination test I:896; VDRL negative. X-rays of the heart revealed moderate enlargement of the left ventricle without displacement of the barium-filled esophagus in the left anterior oblique position. X-rays of the hands were reported as showing swelling of the soft tissue of the fingers. The clinical impression was that the patient had inactive rheumatic heart disease, with aortic insufficiency and aortic stenosis compensated, and rheumatoid arthritis.

The electrocardiogram taken shortly after admission (May 20, 1958) revealed the presence of a WPW pattern. The P-R interval was 0.10 second and the QRS was 0.14 second (Fig. 1). Daily ECG showed the persistence of the abnormal conduction.

TABLE I

DAY OF DIGITALIZATION	DOSE OF DIGITOXIN (MG.)	ELECTROCARDIOGRAPHIC FINDINGS	HEART RATE (BEATS/MIN.)
1st	0.5	WPW	60–62
2nd	0.5	WPW	—
3rd	0.5	WPW	54–56
4th	0.5	On the afternoon of the fourth day normal beats alternating with abnormal ones appeared	—
5th	—	Again WPW pattern. Pressure on the carotid sinus resulted in the appearance of normal complexes alternating with the abnormal ones	—
6th	—	Alternating complexes	—
7th	0.5	Alternating complexes	—
8th	0.5	Alternating complexes	—
9th	—	Normal ECG pattern	44
10th	—	Normal ECG pattern	—
25th	—	Normal ECG pattern	56

Clinical Experiment.—Mechanical stimulation of the right and left carotid sinuses had no effect on the electrocardiographic pattern. Inhalation of amyl nitrite was equally ineffective, and 2 mg. of atropine sulfate given intravenously had only a temporary effect on the heart rate. Then the patient was given a daily oral dose of 0.5 mg. of digitoxin for 4 days. Electrocardiograms were taken daily. On the afternoon of the fourth day, following the administration of digitoxin, regularly reccurring normal complexes with a P-R interval of 0.20 second and a QRS time of 0.08 second were noted (Fig. 2,*B*). On the fifth day a repeated tracing revealed again the abnormal mechanism (Fig. 3,*A*). The heart rate now was 50-52 compared to 60-62 in the control tracing before digitalization (Fig. 2,*A*). Carotid sinus stimulation was repeated. Pressure on the left side was without results; pressure on the right side, however, resulted in normal complexes alternating with the abnormal ones (Fig. 3,*B*). When pressure was released, the ECG continued to show both mechanisms (Fig. 3,*C*). This intermittency of the normal with the abnormal beats continued for the next 4 days. No digitalis was given on the fifth and sixth days. On the seventh

and eighth days an additional daily oral dose of 0.5 mg. of digitoxin was administered. The following day (ninth day after digitalization was instituted) the ECG returned completely to normal (Figs. 4 and 5). The heart rate was regular sinus with 44-46 beats per minute, the P-R interval was 0.23 second, and the QRS time was 0.08 second. No further digitalis was given, and the ECG remained normal until the patient left the hospital two weeks later. At that time the heart rate was 56 per minute, the P-R interval measured 0.20 second, and the QRS was 0.08 second. Table I summarizes the clinical experiment.

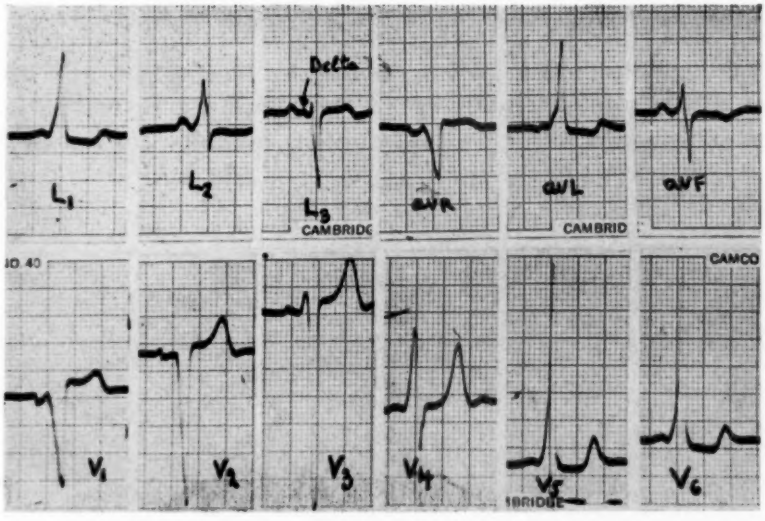

Fig. 1.—ECG taken shortly after admission (May 20, 1958) is typical of the WPW syndrome. In Lead L_3 the *Delta* wave appears as a distinct deflection between the P wave and the QRS complex.

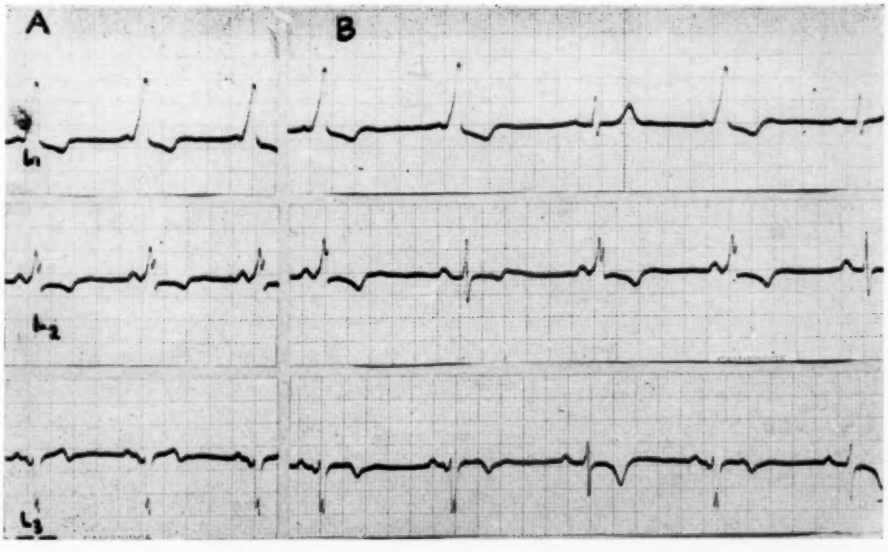

Fig. 2.—Leads L_1, L_2, L_3. *A*, Before digitalization. Heart rate, 62 per minute. *B*, Fourth day after the administration of digitalis. Regularly recurring normal complexes appeared in the ECG (see text). The configuration of the P waves both in the normal and abnormal beats is the same, indicating that the origin of the impulse is the same: sinus.

THE EFFECT OF DIGITALIS ON THE WPW SYNDROME

The effect of digitalis on the syndrome was first noted by Scherf and Schönbrunner.[9] They observed an increase in the duration of the abnormal QRS complex after the administration of the drug, and ultimate disappearance of the abnormally conducted beats when the drug was continued. They concluded that the abnormal conduction mechanism is more susceptible to the effect of digitalis than is the specific conduction tissue.

Fox and associates[10] reported a more detailed study regarding the effect of digitalis on the syndrome. An increase in the duration of the QRS complex was noted following the administration of the drug, and this increase was abolished by atropine. They concluded that the action of digitalis was a vagal effect and that the drug had a greater affinity for the normal than the anomalous atrioventricular pathways.

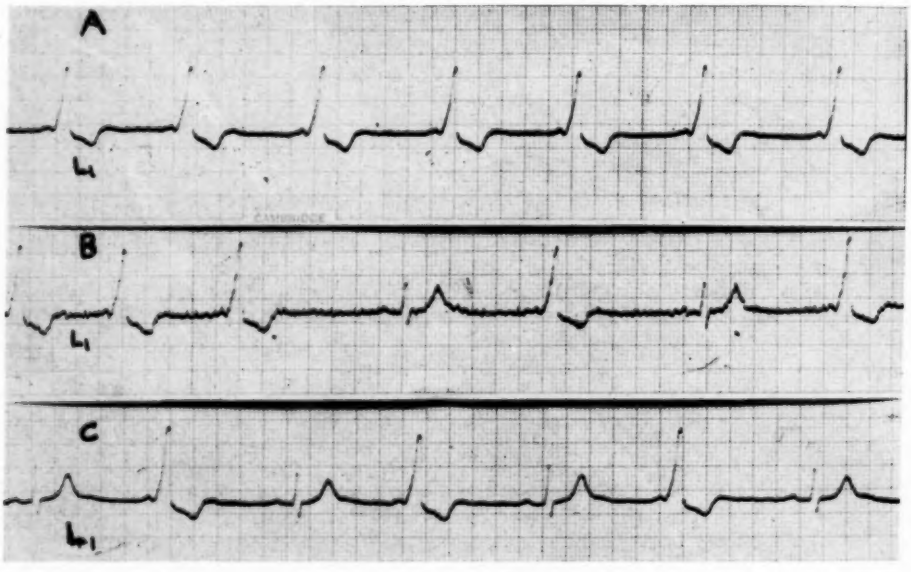

Fig. 3.—Lead L_1. Fifth day after the administration of digitalis. *A*, The ECG is again abnormal (WPW). Heart rate, 55-57 per minute. *B*, Right-sided carotid pressure induces normal complexes alternating with the abnormal ones. *C*, Thirty minutes later the ECG continues to present both mechanisms.

In a later publication, Fox and Bobb,[6] reporting their experience with another case of WPW syndrome, noted that no widening of the QRS was seen following the administration of digitalis. However, if digitalis was administered at a time when the aberrant conduction tissue was depressed by quinidine, and the conduction pattern was normal, it caused the reappearance of the abnormal complexes.

Movitt[11] observed that digitalis seemed ineffective in slowing the ventricular rate in a case with atrial fibrillation and preservation of the abnormally long and aberrant QRS complex during the period of arrhythmia. He concluded that digitalis may be ineffective in slowing conduction through the abnormal pathway between the atria and the ventricles.

Wolff and White[12] noted morphologic changes in the anomalous complex following digitalization, which were not abolished by atropine, and observed a variable effect on the several electrocardiographic intervals. They also observed the failure of digitalis to block the anomalous mechanism in cases of atrial fibrillation with "fast runs" of anomalous beats. The latter were abolished by quinidine. They concluded that these facts are inconsistent with the notion that digitalis suppresses the anomalous conduction.

In the case of Blinder and associates[7] the administration of digitalis produced also a greater aberrancy in the configuration of the QRS, with an increase in the

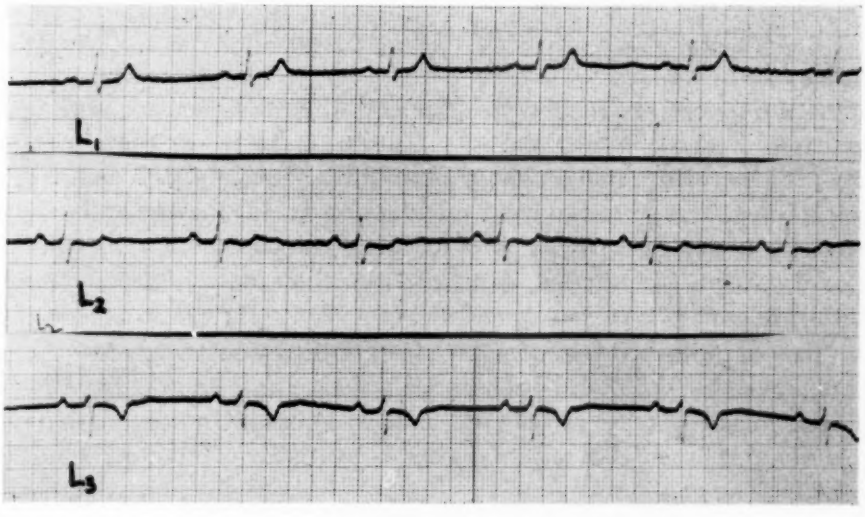

Fig. 4.—Leads L_1, L_2, L_3. ECG 9 days after the administration of digitalis. There are only normal complexes. The P-R interval is 0.23 second, and the QRS time is 0.08 second. Heart rate, 46-48 per minute.

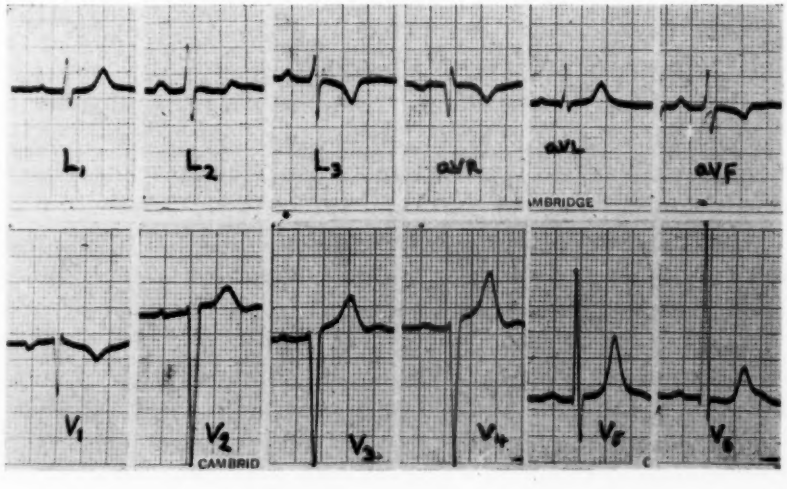

Fig. 5.—Complete ECG after the restoration of normal conduction.

P-J interval which was attributed to a decreased conductivity through the normal pathways following the administration of digitalis.

In a later publication, Wolff and Richman[13] reported a case of WPW syndrome in which at the time of normal conduction, following rapid oral digitalization, abnormal beats appeared spontaneously now and then, or could be induced to appear easily with carotid sinus stimulation. Twenty-one hours after digitalization was started, anomalous conduction prevailed but could be easily interrupted by a deep inspiration. They concluded that the drug produced a critical level of vagal tone, so that the slightest increase (carotid sinus stimulation) induced anomalous conduction, and the slightest decrease (deep inspiration) abolished the abnormal mechanism.

COMMENT

From the foregoing discussion it appears that the effect of digitalis in the various cases of WPW syndrome is not uniform. It seems that in some cases digitalis produces morphologic changes in the abnormal QRS complex, and in others it perpetuates the abnormal conduction or, if the latter is suppressed, facilitates its appearance; in a third category of cases, digitalis has no effect whatsoever, and in still others it suppresses the abnormal conduction and restores a normal mechanism.

In the case presented herewith the effect of digitalis was exactly the opposite of that observed by Wolff and Richman,[13] but the same as that in Scherf's case,[9] although no initial increase of the QRS time was noted. On the fourth day following the daily oral dose of 0.5 mg. of digitoxin, normally conducted beats appeared on the ECG. The configuration of the P waves in both the normal and abnormal beats was exactly the same, indicating that the origin of the impulse was the same (sinus). The P-R interval in the normal beats measured 0.20 second and the QRS time was 0.08 second. The following day, however, the ECG again became abnormal. At that time right-sided carotid pressure was effective in inducing normal complexes which alternated with the abnormal beats, even when the carotid pressure was released. When two more doses of 0.5 mg. of digitoxin were given, the ECG displayed only normally conducted beats.

It is rather obvious that digitalis in this case was responsible for the reversal of the ECG to normal. Either this was due to a direct suppressive effect of digitalis on the abnormal pathway, or it was brought about through some other mechanism (see below). Two points are of particular interest: (1) It should be noted that besides slowing the heart rate, which was probably a vagal effect, digitalis had a direct effect on the A-V node and the normal conduction system. This is indicated from the fact that the P-R interval increased from 0.20 second in the normally conducted beats, when it first appeared, to 0.23 second, five days later (ninth day of the experiment) (Fig. 4) following the administration of an additional 1 mg. of digitoxin. At that time the ECG displayed only normally conducted beats. In other words, despite the fact that the A-V block increased, the abnormal pathway was completely abolished. (2) On the fifth day of the experiment, when the patient had received 2 mg. of digitoxin, and at a time when the abnormal pathway

was present, right-sided carotid pressure induced normal complexes, with no change in the basic sinus mechanism, whereas the same maneuver was ineffective before the administration of digitalis. This indicates that the abnormal pathway was under the influence of the vagus nerve and that its sensitivity increased following the administration of digitalis.

These two points would suggest that there is some sort of connection between the abnormal pathway and the normal conduction system. If we assume, for example, that the abnormal pathway over which the impulse bypasses the A-V node arises in the uppermost part of the node, traversing only a narrow region of the latter, this situation may not interfere substantially with the abnormal conduction under normal circumstances; however, after the administration of digitalis the abnormal pathway could be suppressed because of the action of the drug on the A-V node, and, thus, interrupt the abnormal mechanism. This could explain the restoration of the normal mechanism in the face of increasing A-V block, and it is consistent with the fact that carotid sinus pressure was effective in eliciting normal complexes only after previous sensitization with digitalis.

If this hypothesis concerning the action of digitalis in our case is correct, it becomes apparent that failure or success of the drug in suppressing the abnormal conduction is not a matter of specificity for one or the other pathway, but depends rather on the structure, origin, and direction of the abnormal connection.

The amount of digitalis given could also be an additional contributory factor. In our case the complete salutary effect occurred when 3 mg. of digitoxin had been given over a one-week period.

SUMMARY

A case of WPW syndrome is presented in which the administration of digitalis interrupted the abnormal conduction and restored a normal mechanism.

A review of the literature reveals a difference of opinion concerning the action of digitalis on this syndrome, most of the investigators believing that digitalis facilitates the appearance of the anomalous conduction, or, if the latter is already present, perpetuates it.

On the basis of the present experiment an opinion is expressed regarding the action of digitalis on the WPW syndrome.

I wish to express my appreciation to Dr. D. Scherf and Dr. K. Crispell for their permission to publish the case and for reading the manuscript, and to Dr. R. Rosenblum for his valuable criticism.

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Review

Cor Triatriatum

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INTRODUCTION

"Cor triatriatum" is a rare congenital malformation of the heart, in which a septum stretches in a transverse or oblique plane through the left atrium, thus separating it into two compartments. The upper one connects with the pulmonary veins, and the lower one connects with the left ventricle. In Patten and Taggart's case,[33] however, such an anomalous septum was placed in a vertical plane. In addition, cases with anomalous cords and reticula have become known.[1,14,19,29,39] Finally, four cases[10,15,23,42] have been reported in which the *right* atrium was divided into two compartments by an anomalous septum (cor triatriatum dexter). With the rapid development of cardiac surgery, clinical recognition and correct diagnosis of "cor triatriatum" can now benefit patients with this rare congenital heart disease also. Already, five cases[3,24,*25,44] of successful repair are known.

In the files of the Department of Pathology of the Children's Hospital, University of Buffalo, are included four cases of "cor triatriatum" among 3,740 necropsy examinations from June 15, 1936 to Dec. 31, 1958. This report will present the clinical and anatomic data on these four cases, with a review of the pertinent literature.

CASE REPORTS

CASE 1. (No. 165).—This was a 5½-month-old boy, measuring 61 cm. in length. No clinical data were available. The patient expired on April 5, 1937.

Autopsy Findings.—The autopsy showed that he had had congenital heart disease with widely open foramen ovale and with separation of the left atrium into two individual chambers. The lower chamber alone was in connection with the left ventricle and contained the left auricle and an upper recessus leading into the right atrium, just above the foramen ovale, apparently through an interatrial septal defect. The bilateral pulmonary veins entered into the upper chamber of the left atrium, which appeared to be entirely collapsed and had no direct connection with the

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*Dr. Lam has operated on five patients with a triatrial heart, two of them successfully.

left ventricle. There was unusually marked hypertrophy of the right ventricle. The interventricular septum was intact. The ductus arteriosus was closed. The right atrium was markedly distended, as was the coronary sinus. The entire heart filled out part of the left pleural cavity, compressing the lower lobe of the left lung. There was generalized congestion of the liver, spleen, and kidneys. No slides for microscopic study of the heart were available.

CASE 2 (No. 1816).—The child, a 2½-year-old white boy, was admitted with complaint of dyspnea, cough, fatigue, and cyanosis. Family history was not remarkable. The boy had been apparently well until 2 months previously, at which time he became irritable and fatigued. The mother stated that during the day he would just sit on the floor and cry frequently. When out-of-doors, instead of playing, he would merely stand still and cry. He no longer cared to play or ride his bicycle. These symptoms were sudden in onset and had not been preceded by an upper respiratory infection. During the 6 months prior to admission, the child had had a mild cough, but it had not bothered him excessively. Only more recently had the cough become progressively worse. The child had always been pale, but the parents denied that he had ever been cyanotic. Cyanosis had been noticed only for the previous 2 days.When he was seen by a physician because of his recent illness, the diagnosis of congenital heart disease was made for the first time. For the preceding 2 months the child had received vitamin capsules and an iron tonic. During the previous week his dyspnea had become more severe and he breathed quite rapidly. There were occasional episodes of vomiting. He had no fever, but a poor appetite; only fluid was taken fairly well. There was no history of epistaxis or joint pains.

Physical examination on admission revealed an emaciated, dyspneic, cyanotic boy in acute distress. The extremities were cold and blue. Temperature was 98° F., pulse was 116, respirations were 70. Venous pressure was 200 mm. Hg, and blood pressure was 90/0 mm. Hg. There was cyanosis over the extremities and about the lips, but no adenopathy. The head was well formed. Ears, nose, and throat were negative. The neck was supple. The anteroposterior diameter of the chest was increased and there was a large precordial bulge. The lungs were resonant but there were fine inspiratory râles scattered over the lung fields. The heart was enlarged to the left. The rate was not very rapid and the rhythm was regular. There was a harsh systolic murmur over the entire precordium, heard best at the apex. The abdomen was soft. The liver was palpable 4 cm. below the costal margin. The spleen was not felt. There was no edema, swelling of the joints, or clubbing of the fingers. Femoral pulses were palpable.

The impression on admission was that the child was in heart failure, probably on the basis of a congenital cardiac anomaly. The possibility of rheumatic heart damage was not excluded. In addition, subacute bacterial endocarditis, with a slight degree of bronchopneumonia superimposed upon congested lungs, was considered.

Laboratory studies revealed a blood hemoglobin of 10 Gm., R.B.C. of 3.4 million, W.B.C. of 26,000, P.M.N. of 56 per cent, and 44 per cent lymphocytes. The hemoglobin finally fell to a level of 8 Gm. The white count dropped to 14,000, but a definite polymorph response was maintained. Urinalysis on several occasions gave no abnormal findings. Cultures of the nose and throat grew pneumococci predominantly. A blood culture was sterile. X-ray of the chest showed a homogeneous density at the base of both lungs. The configuration of the heart, enlarged to the right and left, seemed to indicate a congenital anomaly. The ECG was normal at first, but a repeat ECG, following medication with digitalis, revealed a shortening of the Q-T interval and a lowering of the amplitude of the T_2 wave. This was felt to be probably a digitalis effect. Successive electrocardiograms gave a similar picture.

Course and Treatment.—The patient was under digitalis medication throughout his hospitalization. He also received penicillin every day and mercurial diuretics on alternative days. From his fourth hospital day until the day of his death, he was given sulfadiazine. He was kept in an oxygen tent throughout his hospitalization. On the second hospital day, marked improvement was noticed. Although the child was still cyanotic, his respirations seemed to be more regular and less labored. The cough had subsided and the liver had receded in size. While he was in oxygen, his color was fairly good, but he became cyanotic whenever removed from the oxygen tent. The cardiac murmurs persisted, and a continuous gallop rhythm developed. While receiving mercurial diuretics, he lost 2 pounds through elimination of edema fluid. He was afebrile for the first 3 days in the hospital, but on the fourth day he began to spike a fever which persisted between 101° and 103° F. for the next 4 days. Terminally, the fever gradually decreased. The child's condition

deteriorated, and he became weaker and more irritable. The dyspnea increased, and the liver was palpable 4 to 5 cm. below the costal margin. The patient expired on the ninth hospital day, in cardiac failure (Dec. 15, 1948).

Autopsy Findings.—The autopsy showed that he had had congenital heart disease, with a two-chambered left atrium containing a separate upper compartment into which all four pulmonary veins entered. This portion, lined by markedly fibrotic endocardium, was almost entirely divided from the lower supravalvular part of the left atrium. The endocardial fibrosis extended into the pulmonary veins to the point at which they joined the atrium. The upper compartment appeared as a sac within the left atrium and communicated through a short narrow channel of about 4 mm. in diameter with the lower compartment of the atrium. Only this lower portion connected through a slit-like opening (foramen ovale) with the right atrium. There was no communication between the upper compartment, in which the pulmonary veins entered, and the right atrium. Thus, this narrow channel between the almost entirely closed-off sac-like upper portion of the left atrium and an apparently normally built mitral ostium represented, actually, a very marked "supravalvular mitral stenosis." The ductus arteriosus was closed.

The lungs showed an extreme degree of chronic passive congestion, with cyanotic induration, and with a huge congestive infarction in the left lower lobe, with hemosiderin pigmentation. There was considerable edema of the mediastinum, and marked hyperemia and hyperplasia of the bronchomediastinal lymph nodes. The liver was considerably enlarged and congested, as was the spleen. There were numerous recent petechial hemorrhages throughout the mucosa of the gastrointestinal tract.

The final diagnoses included: cor triatriatum with "supravalvular mitral stenosis," extreme hypertrophy of the right ventricle, chronic passive congestion of the lungs, and passive hyperemia of the liver, spleen, and gastrointestinal tract.

CASE 3 (No. 2317).—One month prior to his death, this 3-month-old boy had had a routine checkup by his private physician. At the time of the examination he was found to be well nourished, no heart murmur was heard, and there were no other abnormal findings. He was again brought to his family doctor's office because of a cold. The parents did not consider the baby to be very ill. However, the admitting secretary noticed some cyanosis and dyspnea, and the baby was taken to the examining room immediately. The heart sounds were faint and rapid. The liver extended down to the umbilicus. During the examination the child stopped breathing. Adrenalin, given intracardially, and artificial respirations were without avail.

Autopsy Findings.—The heart was distinctly enlarged. Dissection of the heart revealed the following abnormalities: The anterior surface was formed almost entirely by the right ventricle, which appeared to be markedly hypertrophic and moderately dilated. When the left atrium was viewed, it was obvious that the pulmonary veins entered into a separate compartment, which was somewhat bulging in a sac-like fashion over the lateral wall of the left auricle. A probe through this sinus-like distention at the junction of the pulmonary veins led through a narrow channel into the left ventricle. The entire wall of the sac-like structure was distinctly thicker than the walls of the pulmonary veins. The opening in the anomalous intra-atrial septum measured 4 mm. in diameter. The remainder of the left atrium, reduced by about two thirds of its volume, had a normal auricular appendage and connected through a narrow, funnel-shaped channel (3 by 2 mm., which actually represented the foramen ovale) with the right atrium. The endocardium surrounding the common sinus at the junction with the pulmonary veins was slightly fibrotic; in the lower compartment of the left atrium it was not thickened. The mitral ring was delicate but of normal size. The left ventricle was comparatively small. There was extreme hypertrophy of the right ventricular wall, measuring 0.6 cm. in the pulmonary conus and between 1 and 1.2 cm. in the anterior wall. There were no other anomalies present. The ductus arteriosus was completely obliterated and calcified. The thickness of the left ventricular wall was between 4 and 6 mm. The coronary sinus was in normal position and not dilated. All systemic veins were moderately distended and contained only fluid blood. The individual heart valves were delicate. The blood in the heart chambers was in a fluid state. The right atrium and ventricle were distinctly distended by fluid blood.

CASE 4 (No. 3519).—A white baby girl, aged 3 months, the youngest of five siblings, was born, after a full-term gestation and 2 days of labor, by difficult forceps delivery with face pre-

sentation. The infant cried and breathed spontaneously. No resuscitation or suction was necessary. Birth weight was 7 pounds and 13-¾ ounces. At the age of 7 weeks, the baby was hospitalized with fever and rapid respiration. Chest x-ray showed increased vascular markings, slight enlargement of the heart, and pneumonia. Culture from nose and throat revealed hemolytic streptococci.

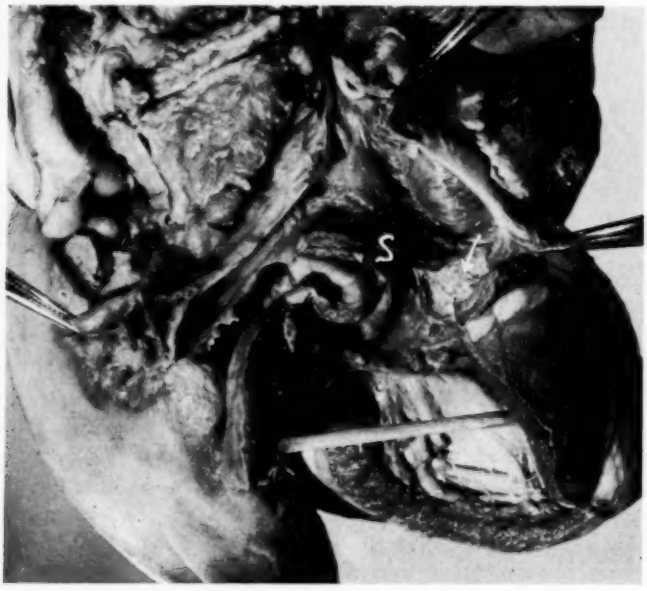

Fig. 1.—Case 3. The lateroposterior view of both upper and lower chambers of the left atrium. The bilateral pulmonary veins enter into the upper chamber. There is a small opening in the intra-atrial septum (*S*), as indicated by the arrow. The intra-atrial septum was cut lateroposteriorly through an opening.

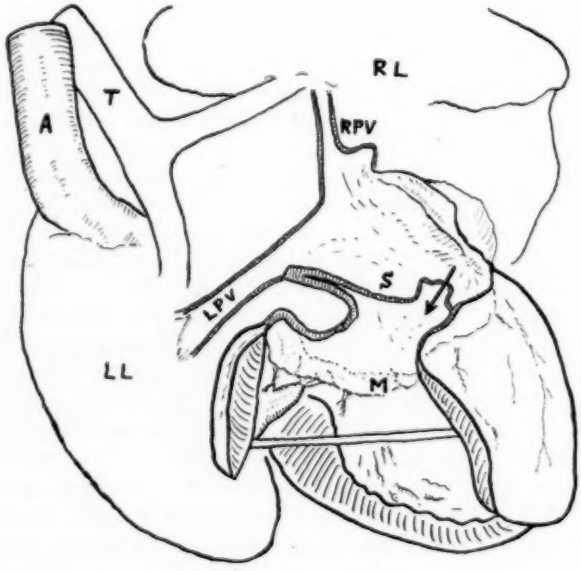

Fig. 2.—Case 3 (schematic view). *LPV:* Left pulmonary vein. *RPV:* Right pulmonary vein. *S:* Intra-atrial septum. *M:* Mitral valve. *LL:* Left lung. *RL:* Right lung. *T:* Trachea. *A:* Descending aorta, anterosuperiorly pulled up.

At the time of admission, the infant's lips appeared to be cyanotic. No murmurs were heard. The liver was palpable. The ECG* showed marked right ventricular hypertrophy, with strain pattern on the precordial lead. Because of heart failure, symptomatic therapy with digoxin, oxygen tent, and antibiotics was initiated. Later, watery stools were noticed.

Fig. 3.

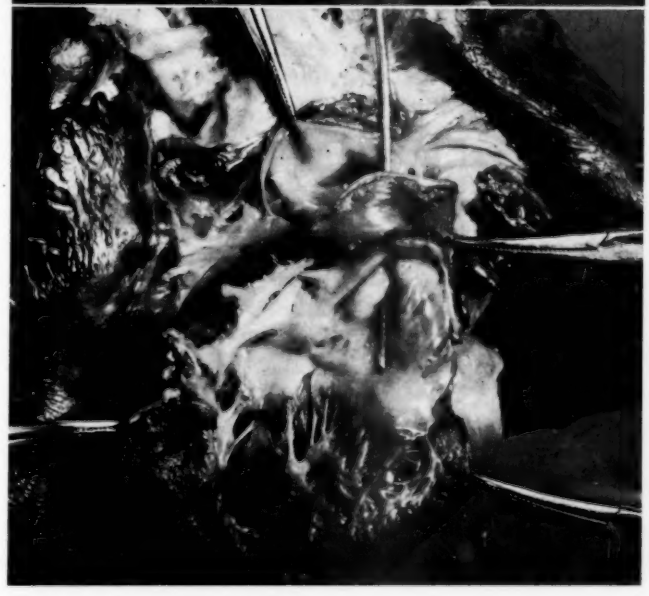

Fig. 4.

Fig. 3.—Case 4. Posterior view of the heart. The upper chamber of the left atrium is opened posteriorly. The bilateral pulmonary veins enter into the upper chamber.

Fig. 4.—Case 4. Anterior view of the left atrium and ventricle. The left ventricle is anterolaterally opened. The normal mitral valves are seen. A thin probe is inserted through a minute opening in the intra-atrial septum from the upper chamber to the lower chamber of the left atrium.

***Data will be published in detail by Dr. P. Vlad and Dr. E. Lambert.**

On the thirteenth hospital day, catheterization* was carried out. For the purpose of angiocardiographic study,* 7.5 c.c. of 70 per cent Diodrast was injected via cardiac catheter into the pulmonary artery. Immediately following the injection of dye the patient became apneic. Intubation was carried out at once. In spite of an intracardiac injection of adrenaline and open-chest heart massage, the child expired (Feb. 4, 1958).

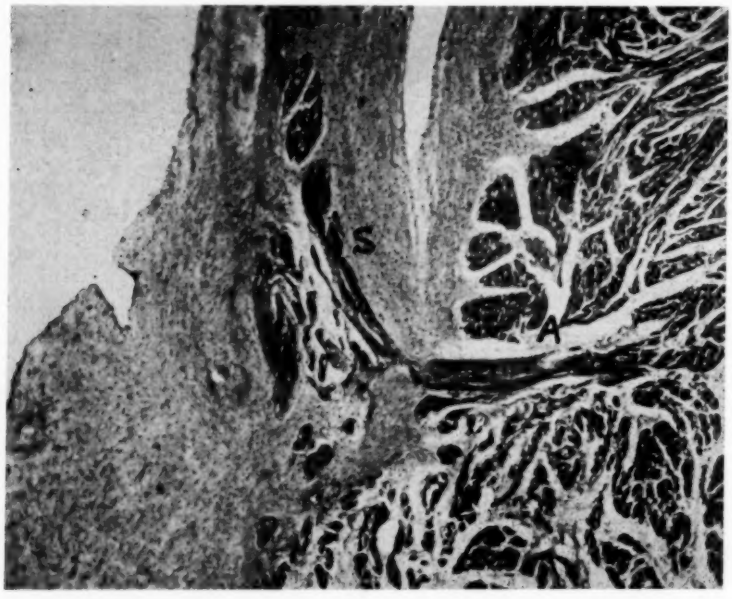

Fig. 5.—Case 4. Posterior wall of the left atrium at its junction of the upper and lower chambers. Typical cardiac muscle fibers in the anomalous intra-atrial septum (*S*) show a direct connection with those of the posterior wall of the atrium (*A*).

Autopsy Findings.—This was a well-developed, well-nourished, 3-month-old white girl. The pericardial sac contained a small amount of blood-tinged fluid. There were scattered petechial hemorrhages in the anterior wall of the left ventricle, and also along the proximal portion of the pulmonary artery. The heart was enlarged, particularly the right ventricle, and measured 5.8 cm. transversely and 4.8 cm. vertically. The left atrium had two compartments. The upper one received both pulmonary veins, its posterior wall measuring 2 to 3 mm. in thickness, with a vertical diameter of about 12 mm. The anterior inferior compartment included the patent foramen ovale and connected directly with the left ventricle through the mitral ostium. The thin diaphragm between both compartments lay in an oblique plane, from an anterior upper position directed downward posteriorly. There were two minute openings in the lower part of the diaphragm between the two compartments; each opening admitted a thin probe. The foramen ovale measured about 2 by 3 mm. The left ventricle measured 7 to 8 mm. in the anterior, and 6 mm. in the posterior, wall. The right ventricle was markedly dilated and hypertrophied, being 11 mm. thick in the anterior, and 6 mm. in the posterior, wall. The valves were regular, having the following circumferences: tricuspid, 4.3 cm., pulmonic, 2.3 cm., mitral, 3.6 cm., and aortic, 1.7 cm. The ductus arteriosus showed minute patency. The coronary sinus was not remarkable.

Findings in the lungs included patchy atelectasis, recent pneumonia, and lobular hemorrhage.

Microscopic Findings.—Heart: The hearts of Cases 3 and 4 were examined histologically. The intra-atrial septal wall, which divided the left atrium into the two chambers, was covered by a thickened fibrous endocardium and con-

*Data will be published in detail by Dr. P. Vlad and Dr. E. Lambert.

tained a thin layer of typical cardiac muscle in the central portion. Two sections were taken from the intra-atrial septum. Each showed clearly the contiguous connection of the cardiac muscle bundles in the diaphragm-like septum with those of the posterior atrial wall. *Lung:* The arterioles and small arteries of the lungs showed distinct thickening of their walls, especially of the media in Case 4. In Cases 2 and 3 this change was less marked (section was not available from Case 1). In addition, there was some intra-alveolar hemorrhage, activation of macrophages, and slight thickening of the alveolar walls. The findings were similar to those seen in mitral stenosis.

DISCUSSION*

The anomaly of stenosis of the common pulmonary vein, known as "cor triatriatum," is one in which the pulmonary veins empty into an accessory chamber attached to the dorsal aspect of the left atrium. Loeffler,[26] in 1949, divided these cases into three groups: (a) No connection exists between the accessory chamber and the left atrium. This accessory chamber might connect with the right atrium, or some of the pulmonary veins might drain in anomalous fashion. Patients with this type of defect usually die in infancy. (b) There are one or several small openings in the intra-atrial septum separating the two compartments of the left atrium. This type was observed only in infants or children, with the exception of the case of Borst,[5] a 38-year-old kyphoscoliotic woman who died with the symptoms of mitral stenosis. The opening in the intra-atrial septum measured 1 cm. in diameter. (c) The accessory chamber communicates widely with the left atrium. Patients with this type may live their full span of life.

A new attempt at further subclassification is made in this study, together with a review of the reported 33 cases, in order to understand better the precise anatomic picture of this anomaly. Moreover, I feel that such a study might be useful for clinical diagnostic purposes, particularly in regard to catheterization and for the surgical approach, as seen in Table I. Special attention is given to the position of the anomalous septum in relation to the foramen ovale and to the size of the opening in the anomalous septum. It is very important to analyze whether the upper left atrial chamber communicates with the lower part of the left atrium, or whether the right atrium connects with the upper anomalous chamber or the lower compartment of the left atrium, because the results of cardiac catheterization and angiocardiography will vary accordingly.

The four cases of this study bring the number of reported cases to a total of 37. These will be discussed briefly as to sex incidence, age, anatomic data of the atrium proper, and relation of the anomalous septum to the foramen ovale and the atrial chamber of the heart.

1. *Sex Incidence.*—Twenty-one patients were males and 14 were females (ratio 1.5:1.0); in 2 cases the sex was not stated.

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*The five surgical cases of Dr. Lam[24] were omitted in this discussion except for surgical operative data, because no detailed anatomic data are available in his report.

2. *Age.*—Fifteen patients were less than 6 months old, and 18 were less than 16 months old. (The survival of the patients is dependent on the position and size of the anomalous septum and its relation to the patent or closed foramen ovale or to an associated atrial septal defect.) (See Fig. 6.)

3. *Relation of the Anomalous Septum to the Foramen Ovale.*—In 12 out of 16 cases the foramen ovale was patent, with the anomalous septum *above* the level of the foramen. In the remainder of this group the foramen ovale was closed. Of the 6 cases with the anomalous septum *below* the level of the foramen ovale, in only 2 cases was the foramen patent. In another group of 3 cases the anomalous septum connected with the foramen ovale at its center; in one of these cases, in particular, (William and Abrikosoff[45]) the medial edge of the septum was divided into two limbs which enclosed the foramen ovale. In the remaining 12 cases no accurate information on the relationship between the anomalous septum and the foramen ovale could be obtained, except that in one of them the foramen ovale was patent, and in 8 cases it was closed. The three remaining cases of this group were those in which a successful surgical operation was carried out.

TABLE I. CLASSIFICATION OF COR TRIATRIATUM

I. Cor triatriatum with no opening in the anomalous intra-atrial septum:
  A. Patent foramen ovale in the lower left atrial chamber:
    1. With connection between the right atrium and the upper left atrial chamber (septal defect)[17] (Case 1 of this report)

II. Cor triatriatum with small opening(s) in the anomalous intra-atrial septum:
  A. Patent foramen ovale:
    1. In the upper left atrial chamber[27,31]
    2. In the lower left atrial chamber[8,9,21,30,33] (Cases 2, 3, and 4 of this report)
    3. Incomplete description of the position[36]
  B. Closed foramen ovale:
    1. In the upper left atrial chamber[5,11,37,40]
    2. Between both upper and lower left atrial chambers[18,21,45]
    3. In the lower left atrial chamber[4,28]
    4. Incomplete description of the position[2,12,34,35,38,41]
  C. Surgically operated cases (minute patency?)[3,25,44]

III. Cor triatriatum with wide opening in the anomalous intra-atrial septum:
  A. Patent foramen ovale in the lower left atrial chamber[13]
  B. Closed foramen ovale in the lower left atrial chamber[7,16]
  C. Closed foramen ovale: incomplete description of the position[26]

4. *Pre-Formed Anatomic Openings (Foramina) Within the Anomalous Septum.*—The circulatory disturbance in the pulmonary circuit was influenced by the absence or presence of one or more openings in the anomalous septum and also by the size of such openings. In 3 cases the anomalous septum was intact, not providing for a direct communication between the upper and lower chambers in the left atrium. Of 30 cases, there was a single small opening within the intra-atrial septum in 24, and a few small foramina in the remaining 6. A large opening in the anomalous septum was found in 4 adults. Data as to the relationship of the size of the foramen or foramina in the anomalous septum to the survival

age were available in 31 cases. In 11 (35.5 per cent) of these a foramen was altogether absent or smaller than 3 mm. in diameter. In another 11 cases (35.5 per cent) the diameter varied from 3 to 6 mm. In the remaining 9 cases (29 per cent) the foramen within the intra-atrial septum had a diameter of over 7 mm. Patients having a foramen in the anomalous septum of less than 3 mm. in diameter showed a mean age of 3.3 months, whereas those in whom this foramen was wider than 3 mm. had reached a mean age of 16.1 years.

5. *Relation of the Accessory Upper Chamber of the Left Atrium to Other Chambers of the Heart.*—In Stoeber's[43] case the upper accessory chamber of the left atrium did not communicate with the right atrium. The bilateral superior pulmonary veins, however, opened into the right atrium, which, through a slit-like foramen ovale, was thus connected with the lower compartment of the left atrium.

In 2 other cases without any opening in the anomalous septum the right atrium connected with the upper accessory chamber through an interatrial septal defect and, in addition, communicated through a patent foramen ovale with the lower compartment of the left atrium.

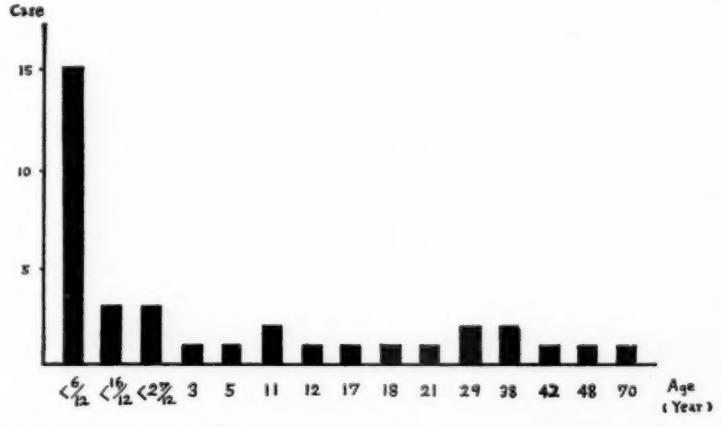

Fig. 6.—Age distribution of the patients with cor triatriatum (36 cases). Age unknown in one case.

In one[31] of 30 cases with a small opening in the anomalous septum the accessory upper compartment of the left atrium had a direct communication with the right atrium through a patent foramen ovale, measuring 1 by 2 cm. in diameter. The cyanosis which was already present at birth, and which became constant and more marked in the terminal state, can be explained on the basis of the widely patent foramen ovale, consistent with the anatomic evidence of a hypertrophic right ventricle, 8 mm. in thickness.

In 8 of 30 cases with a small opening in the anomalous intra-atrial septum the right atrium communicated with the lower compartment of the left atrium. If in the course of a successful heart catheterization, this lower compartment of the left atrium is entered, an elevated pulmonary capillary (wedge) pressure and a normal left atrial pressure will be obtained.

In 16 cases with a small opening in the anomalous diaphragm, there was no direct communication between the right atrium and the upper or lower com-

partments of the left atrium. Also, in 2 out of 3 cases with a large opening in the intra-atrial septum, left and right atria were completely separated, because of the absence of a patent foramen ovale. When this detailed anatomic analysis is applied to the 3 cases of this group of 30 in which successful surgical operation was performed, it appears that in 2 of them no mention was made of whether there was a communication between the two compartments of the left atrium. Certainly such a connection must have existed (otherwise blood could not have entered the left ventricle), but it was not discovered by the surgeon's exploring finger. There is, however, the other possibility that blood from the upper intra-atrial chamber could have reached the left ventricle through a small interatrial septal defect and a minute patent foramen ovale.

6. *Structure of the Anomalous Septum in the Left Atrium* (*Table II*).—Knowledge of the histologic structure of the anomalous septum will provide a better understanding of the development of cor triatriatum and furnish more precise information for the surgeon attempting its repair. This septum is composed of cardiac muscle fibers just like those of the posterior wall of the upper compartment. In some cases[2,17,45] these "septal" cardiac muscle fibers are directly connected with those of the atrial wall. In Hagenauer's case[17] the anomalous septum is made up of double layers of cardiac muscle, the upper layer being continuous with the muscular wall of the upper chamber, and the lower layer being continuous with the muscle fibers in the wall of the lower chamber.

In most of the cases, either the muscle fibers of the intra-atrial septum are reported as not being continuous with those of the atrial wall, or no comment is made as to any such connections. However, serial sections probably would reveal the contiguity of the muscle fibers in the anomalous septum with the myocardium of the atrial wall, as described in the third case of this report.

In Parsons' case[32] the upper portion of the interatrial septum which divided the right auricle from the upper chamber of the left auricle consisted of a double layer of cardiac muscle separated by some strands of fibrous tissue. In addition, marked endocardial thickening of the atrial wall has been reported[11,18,26,27] (Cases 3 and 4 of this report). Doxiadis and Emery[9] describe only loose connective tissue and a few elastic fibers in the anomalous septum and small areas of endocardial fibroelastosis in the auricle, on the upper surface of the mitral valve and in the intima of the pulmonary veins (but not in the abnormal septum). In Nash and MacKinnon's case[30] there was no fibroelastosis.

Calcium deposits have been reported in 4 cases.[5,18,*34,44] From the surgical point of view, the case of Pedersen and Therkelsen[34] (1954) is interesting. The surgeon failed to find an anomalous septum which, as revealed post mortem, had an opening of 5 by 7 mm. in diameter, with scattered calcifications around its border. At the time of operation, he found, after opening the rather small left auricular appendage, only a normal mitral ostium. In 1956, Vineberg and Gialloneto[44] reported a successful operation for this rare anomaly. The surgeon's exploring finger detected the anomalous septum which contained a calcified area about 2 cm. in diameter.

*It is not clear, however, from this report whether the calcium deposit was in the anomalous septum or somewhere else in the atrial wall.

TABLE II. STRUCTURE OF THE ANOMALOUS SEPTUM IN THE LEFT ATRIUM

AUTHOR	FINDINGS
Borst,[5] 1905	Central calcification
William,[45] 1911	Cardiac muscle bundles in the anomalous septum which were directly connected with those of the posterior wall of both upper and lower compartments. The muscle layers of the upper compartment were thicker than those of the lower compartment
Hagenauer,[17] 1931	Cardiac muscles in the posterior wall of the first and second chambers of the left atrium. Two muscle layers in the septum (intra-atrial)
McLester,[28] 1940	Intra-atrial septum was made up of cardiac muscle fibers separated by fibrous tissue. Muscle predominated at the periphery, but in the center the septum consisted chiefly of fibrous tissue. Both surfaces were covered by endothelium
Loeffler,[26] 1949	Posterior wall of the first left atrium showed cardiac muscles. Connective tissue and cardiac muscles in the anomalous septum. Dense elastic fibers in the endocardium
Parsons,[32] 1950	Anomalous septum consisted of elastic and collagenous tissue interspersed with scattered plain muscle fibers. In the center of the septum, in its outer half only, was a single layer of cardiac muscle, which was completely separated from the muscle in the auricular wall. The interauricular septum in its upper part, where it divided the right auricle from the upper chamber of the left auricle, consisted of a double layer of muscle separated by some strands of fibrous tissue
Edwards,[11] 1951	Collagen, elastic fibers, cardiac muscles in the first and second chambers of the left atrium. The first chamber was thicker than the second. The lining of the first chamber was similar to that of the atrium
Barnes,[2] 1952	Anomalous septum: collagen fibers, cardiac muscles, which appeared to be continuous with those of the auricular wall
Doxiadis,[9] 1953	Anomalous septum: almost entirely loose connective tissue, but a few elastic fibers. It did not appear to be penetrated by muscle from the auricular wall. Small areas of endocardial fibroelastosis on other parts of the auricle and on the upper surface of the mitral valve, showing a similar appearance to the lesions within the pulmonary veins
Pedersen,[34] 1954	In anomalous septum, one opening with scattered calcification around its margin (macroscopic description)
Hartmann,[18] 1955	Left atrium (site?): marked thickening of endocardium to more than ten times its normal thickness. Hyalinized connective tissue. Large focal deposits of calcium near the endocardial surface. No inflammation
Nash,[30] 1956	Anomalous septum was composed of fibrous tissue and cardiac muscle, and the upper and lower surfaces were covered by endothelium. No evidence of fibroelastosis
Vineberg,[44] 1956	Calcification, 2 cm. in diameter, in the anomalous septum (gross finding)
Sawyer,[40] 1957	Anomalous septum: a few fibers of cardiac muscle interposed between two layers of collagenous connective tissue, the latter containing a few elastic fibers
Cottier,[8] 1957	Cardiac muscle layer in the anomalous septum
Maxwell,[27] 1957	Some endocardial thickening
Buffalo Children's Hospital, 1958	Case 3: Cardiac muscles in the anomalous septum connected directly with those of the atrial wall. Endocardial thickening. The posterior wall of the upper atrial chamber was made up of cardiac muscles
	Case 4: Similar to that of Case 3

TABLE III. PULMONARY LESIONS

AUTHOR	SEX	AGE	FINDINGS
Palmer,[31] 1930	M	18 yr.	Slight thickening of the artery wall
McLester,[28] 1940	M	18 yr.	Considerable pulmonary congestion and edema. Bronchopneumonia
Edwards,[11] 1951	F	6½ mo.	1. Dilatation of the alveolar capillaries to varicose proportions: engorgement, strikingly tortuous in some instances 2. Concentric cellular thickening of the wall of the arterioles causing luminal narrowing. Edema of the wall 3. Thickening of the medial layer and prominent internal elastic membrane of the intrapulmonary muscular arteries
Doxiadis,[9] 1953	F	10 wk.	1. Alveolar edema and increased macrophages in the alveoli 2. Hypertrophy of the pulmonary veins and some of the pulmonary arteries 3. Small deformities, sessile intimal thickenings of the veins within the lung substance
Pedersen,[34] 1954	F	29 yr.	Chronic congestion and edema (brown induration)
Becu,[4] 1955	F	5 mo.	1. Extreme capillary engorgement 2. Intra-alveolar hemorrhage and edema 3. Hypertrophy of the media of the large and small muscular arteries. Thickening of the internal elastic layer 4. Lymphatic dilatation of the pleura
Hartmann,[18] 1955	M	12 yr.	1. Several wedge-shaped infarcts 2. Vessels thickened, sometimes lumina obliterated. All layers showing marked proliferation of the connective tissue, but media and adventitia more involved. Some vessels occluded
Sawyer,[40] 1957	F	2 yr. 7 mo.	1. Tortuous, dilated alveolar capillaries 2. Concentrically thickened media with slightly narrowed lumen of the muscular arteries. Moderate amount of fibrous tissue between the endothelium and internal elastic lamina of the larger arteries 3. Extravasation of erythrocytes in alveoli. Edema fluid in alveoli, in some parts. Hemosiderin pigment in macrophages
Maxwell,[27] 1957	M	7 wk.	Widespread arteriolar thickening
Cottier,[8] 1957	M	5 mo.	1. Mostly small alveoli, partly aerated and also atelectatic. Macrophages with hemosiderin or fat. Edema, erythrocytes, many neutrophilic leukocytes with fat. Diffusely thickened interalveolar walls (precollagenous increase) 2. Dilated engorged capillaries 3. Interlobular septum not thickened 4. Artery: no proliferation or thickening of intima or media; nonessential thickening of adventitia 5. Vein: marked dilatation; slight fibrous increase in adventitia
Buffalo Children's Hospital, 1958	M	2½ yr. (Case 2)	1. Brown induration. Edema of interlobular connective tissue and alveoli. Macrophages with hemosiderin pigments 2. Slight medial thickening of small arteries
	M	3 mo. (Case 3)	1. Marked congestion and intra-alveolar hemorrhages. Many macrophages 2. Slight thickening of the media of the small arteries
	F	3 mo. (Case 4)	1. Intra-alveolar hemorrhages, edema, and activated macrophages 2. Distinct thickening of the media and adventitia of the small to medium-sized arteries

F. C. Helwig[19] reported a case with a hammock-like, fenestrated band suspended in the roof of the left atrium, having a histologic structure similar to that seen in the anomalous septum of the typical cor triatriatum. This band was covered by a single layer of flat cells, with a dense, more or less homogeneous hyaline zone of almost anuclear fibrous tissue, a looser type of fibrous tissue and rather numerous cardiac muscle fibers forming its substance. On the basis of Helwig's observation, the anomalous reticula of cords appear to be clearly related genetically and histologically to the anomalous septum in the typical case of cor triatriatum.

7. *Pulmonary Lesions* (*Table III*).—Among the clinical symptoms mentioned in the reported cases, respiratory embarrassment secondary to pulmonary congestion is an outstanding feature in patients with cor triatriatum. Hemoptysis is described in 3 cases.[7,18,28] The marked congestion with tortuous, dilated alveolar capillaries and activation of macrophages and extravasation of erythrocytes in alveoli can explain the clinical picture.

Vascular changes, including dilatation and slight thickening of all vessels, especially of the pulmonary arteries, was first mentioned by Palmer,[31] in 1930. Edwards and associates,[11] in 1951, described in more detail such changes as: dilatation of the alveolar capillaries to varicose proportions, concentric cellular thickening of the wall of the arterioles, causing luminal narrowing, thickening of the media, and a prominent inner elastic membrane in the intrapulmonary muscular arteries.

Similar arterial changes were also observed in 8 other cases[4,9,18,27,40] (and Cases 2, 3, and 4 of this report). In the case of Cottier and Tobler,[8] no proliferation or thickening of the arterial intima and media was found. In Hartmann's case,[18] some vessels were occluded, causing several wedge-shaped infarcts.

Doxiadis and Emery[9] described, in a 10-week-old girl, hypertrophy of the pulmonary veins with "sessile" intimal thickenings, and Cottier and Tobler[8] noted markedly dilated veins in the lung tissue, with slight fibrosis of the adventitial layer.

In the case of Becu and associates,[4] there was prominent dilatation of the pleural lymphatics and interlobular septa of both lungs, as observed by some authors in other forms of congenital heart disease, combined with obstruction to the pulmonary flow.

8. *Other Associated Findings.*—The cardiac lesion most commonly associated with cor triatriatum is marked hypertrophy and dilatation of the right ventricle, as found in 26 of a total of 37 cases (70.3 per cent). A dilated right atrium was present in 9 cases (24.3 per cent). The left ventricle was small in 8 cases (21.6 per cent), and a noticeably large atrium was mentioned in 4 cases (10.8 per cent).

A parietal thrombus in the upper chamber of the left atrium was found in 1 case.[35] The ductus arteriosus Botalli was patent in 3 cases (8.1 per cent), whereas in 9 cases (24.3 per cent) the duct was closed, as specifically stated.

A dilatation of the pulmonary artery was present in 6 cases (16.2 per cent), and the pulmonary veins were dilated in 3 (8.1 per cent). The bilateral superior pulmonary veins entered into the right atrium in 1 case.[43] In Patten's case[33]

the pulmonary veins did not drain directly into the right atrium. The right superior pulmonary vein entered in a peculiar manner near the apex of the wedge, astride a small defect in the intra-atrial septum, separating the accessory median from the left atrial chamber, while the remaining branches drained into the median chamber. A persistent left superior vena cava connecting with the left innominate vein was found in Maxwell and associates' case.[27] Becu and associates[4] reported a case of cor triatriatum with marked stenosis of the pulmonary veins causing pulmonary edema and symptoms of pulmonary hypertension. In Palmer's case[31] the pulmonary veins converged to a single vein, which entered the posterosuperior chamber.

The mitral valves were normally developed in the reported cases, with the exception of that of Parsons,[32] in which they appeared to be hypoplastic.

As to the tricuspid valve, only one associated anomaly is reported. In Palmer's case,[31] two of the cusps were fused, producing, in reality, a bicuspid valve.

A high interventricular septal defect with an overriding aorta and stenosis of the pulmonary conus was observed in 2 cases.[38]

Finally, an interatrial septal defect was present in 4 cases. In that of Patten and Taggart,[33] the right atrium connected with the accessory median left chamber below the level of the patent foramen ovale. In 2 cases[17] (and Case 1) the accessory upper chamber connected through an inter-atrial septal defect, whereas the lower chamber connected through the patent foramen ovale with the right atrium. In the fourth case[27] the large interatrial septal defect, 6 by 3.5 mm. in diameter, was found at the level of the foramen ovale in the upper chamber.

9. *Etiology.*—Various theories have been advanced to account for the anomalous intra-atrial septum. (a) The septum is said to be an overgrowth of the valve of the foramen ovale.[13,16,21,37,38] This theory can be easily rejected, since the unaltered foramen ovale is seen in its proper place. (b) The lesion is that of a primary displacement of the main pulmonary vein, and the diaphragm is interpreted as the septum primum of Born, which, owing to an increased intensity of growth, formed the whole final atrial septum. The opening in the diaphragm is the ostium primum.[5,12,33,43] (c) The third theory, which Loeffler[26] has accepted in principle, postulates that the common pulmonary vein has not been incorporated into the left atrium in a normal manner.

In 1896, Griffith[16] stated that there had been a "failure in the complete amalgamation of that part of the atrium which is said to be derived from the confluent portions of the pulmonary veins and that derived from the left-hand division of the common auricle of the embryonic heart."

The anomalous band in the left atrium is probably due to some imperfection in the development of the septum primum (Helwig[19]). Chiari[6] (1905), quoted by Helwig, stated that the cords and diaphragms might be caused by a separation of the primary and secondary septum, thus producing a partial division of the left atrium.

Hagenauer[17] (1931) based his explanation of the malformation on the results of Spitzer's (1923) work on the embryonal development of the heart. He believed that the anomaly is the result of an abnormal junction between the pulmonary vein stem and the primitive heart. He assumed that this junction, instead of

being at a right angle, takes place at an acute angle, so that when the sinus venosus dilates, it compresses the pulmonary vein, the mouth of which is eventually obliterated by adhesions.

From an analysis of the previously recorded cases, Parsons,[32] in 1950, made the assertion that the septum is due to a defect at the junction between the pulmonary vein and the right auricle and is the result of developmental arrest late in the second month of fetal life.

In 1951, Edwards and associates[11] reported 2 cases, one with atresia of the common pulmonary vein, the pulmonary veins draining into the superior vena cava, and the other with stenosis of the common pulmonary vein (cor triatriatum). According to these authors, the accessory chamber into which the pulmonary veins open is, in reality, a dilated common pulmonary vein, and the appearance of an accessory chamber results from failure of the common pulmonary vein to become incorporated into the dorsal wall of the left atrium, as it normally should. They agree with Loeffler that the septum between the accessory chamber and the left atrium is formed by the posterior wall of the primitive atrium. They also stated that the opening in the septum represents the junction of the embryonic common pulmonary vein with the sinoatrial portion of the heart. Primarily, therefore, the malformation represents a developmental arrest at the stage at which the sinoatrial region of the heart shows the evagination which is to become the common pulmonary vein. Sawyer and associates[40] (1957) stated that the most widely accepted hypothesis is that the septum represents a defect in the development of the common pulmonary vein, but that this theory fails to explain the presence of the fossa ovalis in the medial wall of the upper anomalous chamber.

According to Doxiadis and Emery[9] (1953), the histologic findings of abnormalities in the endocardium of the left auricle proper and in the pulmonary veins within the lung suggest that the etiology in their case of cor triatriatum may not be completely explainable on the basis of a single anatomic maldevelopment. It appears more likely to these authors that the anomaly of cor triatriatum is related more closely to other deformities of the endocardium, affecting many parts of the heart; in the past, these deformities were called fetal endocarditis but are now termed endocardial fibroelastosis.

The 2 cases which Preisz[38] (1890) described had, in addition to the anomalous intra-atrial septum, an interventricular septal defect with an overriding aorta and stenosis of the pulmonary conus. These malformations are due to an arrest of growth toward the end of the second month of pregnancy (Keith,[22] 1909). As previously stated, a rare accessory septum subdividing the right auricle is supposed to be due to a defect at the junction between the inferior vena cava and the right auricle, the septum, perhaps, representing a persistent right valve of the sinus venosus.[10,15] Parsons[32] stated that an anomalous septum in the left auricle is compatible with these malformations in the right auricle and may well be of similar origin.

10. *Symptomatology.*—The clinical picture of the patient with cor triatriatum has been neither constant nor characteristic, being conditioned mainly by pulmonary hypertension and congestion, with subsequent right ventricular

failure. Most of the patients died during early childhood; others developed, sooner or later, congestive heart failure leading rapidly to death.

Various types of murmurs have been described thus far in 15 cases: diastolic in 4, and systolic in 12, including 2 cases with both types of murmurs. A presystolic murmur was heard in Borst's case. The precise characterization of the murmurs in relation to the anatomic data is listed in detail in Table IV. The findings of a pulmonary second sound are tabulated in Table V.

In Vineberg and Gialloneto's case,[44] pulmonary edema was present as the first sign. Dyspnea and cyanosis are commonly observed, as is the enlarged palpable liver, as a result of cardiac failure.

Electrocardiographic findings (Table VI): Electrocardiograms have been recorded in 11 patients thus far, including 2 of the 4 patients in this study. The most common finding has been right ventricular hypertrophy.

Radiographic findings (Table VII): As shown in Table VII, a globular or diffuse enlargement of the heart was described in several cases; in some, specically, right ventricular hypertrophy or predominance of the right atrium was reported. There is no characteristic diagnostic radiographic pattern for this rare anomaly, except for some evidence of right heart hypertrophy.

During the same 23-year period in which our 4 cases of cor triatriatum had occurred, there were recorded in the Department of Pathology of the Children's Hospital of Buffalo, 12 cases with congenital lesions of the mitral ostium (atresia or stenosis). Of these, only 3 cases revealed pure mitral lesions without any other cardiac anomaly: atresia, 1 case, stenosis, 2 cases. All 3 of these had a patent ductus arteriosus Botalli, and in 2 the foramen ovale was patent. In the remaining 9 cases, there were such associated anomalies as truncus arteriosus communis, tetralogy of Fallot, and aortic ostium lesions. Therefore, for the purpose of differential diagnosis in general, the fact should be remembered that simple congenital mitral atresia or stenosis, without other cardiac anomalies, and cor triatriatum were rather rare in a large series of necropsy studies (3,740 cases). Total incidence of congenital lesions of the mitral ostium, with or without other cardiac anomalies, was three times higher than that of cor triatriatum in our material. The difficulty of exact clinical recognition of congenital mitral stenosis or atresia is obvious from the analysis of the 12 cases mentioned here: the left atrium was dilated in 3 cases; left atrial hypertrophy was seen in 1 case, whereas 3 cases had a small atrium; the left ventricle was distinctly hypertrophic in 4 cases, hypoplastic likewise in 4, and merely dilated in 1. Eight cases, two thirds of the total, showed distinct right ventricular hypertrophy. These somewhat detailed anatomic data have been added here to stress once more the extreme difficulty in arriving at a definite diagnosis of cor triatriatum from electrocardiographic and radiographic findings alone.

Catheterization Findings (Table VIII).—Parsons,[32] in reporting his case of cor triatriatum in 1950, expressed doubt that catheterization or angiocardiography would be of any help in diagnosis. However, cardiac catheterization studies were carried out in 6 patients with cor triatriatum, with results of some informative value. There was marked right ventricular and pulmonary arterial hypertension. High pulmonary artery wedge pressure has been reported, with

special emphasis on its diagnostic value.[25,35,40,44] Moreover, normal pressure was recorded in the left "proper" atrium, representing the lower intra-atrial chamber,[3,27,34] whereas abnormally high pressure (22 mm. Hg) was found in the left anomalous upper chamber.[3,44] After surgical repair of this intra-atrial septum, normal pressure (5 mm. Hg) was obtained in the upper chamber.[3] The size of the opening in the anomalous intra-atrial septum can be predicted rather closely from data obtained by cardiac catheterization.[34] Sawyer and associates[40] (1957) stated that if the pulmonary capillary pressure is accepted as a reflection of the pressure beyond the pulmonary arterioles, an elevation of this pressure, in the absence of left ventricular failure or of constrictive pericarditis, would suggest some obstruction to the flow of blood from the lungs to the left ventricle. The most common cause of such an obstruction is mitral stenosis. The abnormal intra-atrial septum in cor triatriatum, however, can have the same effect.

I have already called attention to the various anatomic connections with the right atrium in the presence of cor triatriatum. If the anomalous upper chamber communicates with the right atrium through an interatrial septal defect, or through a large patent foramen ovale, with the intra-atrial septum below their level, the predominant hemodynamic change might be a left-to-right shunt as in the Lutembacher complex.[27,31]

In 8 of 30 cases with a small opening in the anomalous intra-atrial septum the right atrium communicated with the lower compartment of the left atrium. In such cases, with the catheter successfully inserted into this lower compartment and, also, into the pulmonary artery, an elevated pulmonary capillary (wedge) pressure but a normal left atrial pressure will be obtained. In 16 reported cases with a small opening in the anomalous diaphragm, there was no direct communication between the right atrium and the upper or lower compartments of the left atrium. Therefore, by the usual cardiac catheterization, the pressure in the left "proper" atrium could not be obtained in these cases.

If the right atrium connects with both the upper and the lower compartments of the left atrium, the catheterization results would probably differ. However, no data, have been obtained as yet in cases of this special kind of cor triatriatum. If anomalous pulmonary venous drainage is associated with cor triatriatum, a rise in the oxygen saturation of the blood taken from the right heart will be obtained.[27]

In the presence of an interventricular septal defect associated with cor triatriatum, no catheterization results have been obtained as yet.

11. *Surgical Operation.*—Due to the rarity of, and great difficulty in diagnosing, cor triatriatum, data on the surgery of this disease are of necessity very limited. Successful operation has been reported in 3 patients: in 2 in 1956, and 1 in 1957. In addition, Lam[24] has operated on 5 patients with a triatrial heart, successfully on 2 of these. In Vineberg and associates' case[44] the left atrium was entered and explored with the index finger, but was closed again when no defect or tumor was palpated. However, on the basis of pressure differentials between the left atrium and the pulmonary vein, the left auricle was reopened and, subsequently, the anomalous septum with calcification was detected. The surgeon then proceeded to make a large opening through this intra-atrial septum.

TABLE IV. STETHOSCOPIC FINDINGS

MURMUR	AGE	INTRA-ATRIAL SEPTUM		FORAMEN OVALE	DUCTUS BOTALLI	R.A.	R.V.	L.A.	L.V.	ASD	REMARKS
		NO. OF OPENINGS IN ANOMALOUS SEPTUM	SIZE OF OPENING								
A. Diastolic Murmur (DM)											
1. Grade II-IV along left border of sternum[44]	21 yr.	?	?	—	—	—	—	—	—	—	PA dilated.* Surgery: calcium in septum, 2 cm. SM
2. Grade I—diastolic runoff[41]	5 yr.	One	5 mm.	Closed	Closed	Large	15 mm.	—	—	—	Heart 260 grams
3. Grade I—mitral diastolic murmur at apex[3]	17 yr.	One	10 x 5 mm.	Closed (?)	—	—	—	—	—	—	*Surgery: calcium deposits
4. Slightly rough blowing murmur over entire precordium during last half of diastole[28]	18 yr.	Two	5 x 2 mm. 5 x 3 mm.	Closed	—	—	6 mm.	—	—	—	Enlarged right heart
B. Systolic Murmur (SM)											
1. Blowing[21]	1 mo.	Several	Various	Closed	—	—	Large	—	—	—	—
2. Loud (tick-tack like)[33]	3 mo.	One	3.2 mm.^{2}	30.2 mm.^{2}	Patent	—	Large	—	—	One-117 mm.^{2}	PA enlarged; heart 51 grams; PV anomalous
3. Loud at apex and transmitted practically throughout chest[31]	3½ mo.	One	Slit-6 mm.	10 x 20 mm.	Patent	—	8 mm.	—	Small	—	PA enlarged. Bicuspid valves in right heart
4. Loud[36]	3½ mo.	One	Thin-probe	Patent?	Patent	—	—	—	—	—	—
5. Grade II[40]	2½ yr.	One	3 mm.	Closed	Closed	Dilated	7 mm.	—	7 mm.	—	Heart 130 grams
6. Grade II[41]	5 yr.	One	5 mm.	Closed	Closed	Large	15 mm.	—	—	—	Heart 260 grams. DM
7. Grade III-IV[44a]	21 yr.	?	?	—	—	—	—	—	—	—	DM. PA dilated.* Surgery: calcium in septum, 2 cm.
8. Grade IV blowing[18]	12 yr.	Two	6 mm. 5 mm.	Closed	—	—	10 mm.	—	8 mm.	—	—
9. Generalized harsh[27]	17 wk.	One	2 mm.	ASD 6 x 3.5 mm.	—	Large	Large	Not dilated	Small	—	Left persistent superior vena cava
10. Generalized harsh (Case 2)	2½ yr.	One	4.5 mm.	Slit	Closed	—	—	—	—	—	—
11. Soft[25]	29 yr.	?	?	Closed?	—	—	—	—	—	—	PA dilated
12. Loud, harsh, long murmur[9]	10 wk.	One	2 x 3 mm.	Patent	Closed	—	4.5 mm.	—	4-6 mm.	—	—
13. Systolic[35]		Few	Narrow	—	—	Dilated	Hyper-dilated	—	—	—	Thrombosis in the first left atrium
C. Presystolic Murmur[5]	38 yr.	One	10 mm.	Closed	—	—	Large	—	—	—	Central calcification

*With a snapping first sound over the mitral area.
PA = Pulmonary artery.

TABLE V. PULMONARY SECOND SOUND

PULMONARY SECOND SOUND (P_2)	AGE	INTRA-ATRIAL SEPTUM		FORAMEN OVALE	DUCTUS BOTALLI	R.A.	R.V.	L.A.	L.V.	ASD	REMARKS
		NO. OF OPENINGS IN ANOMALOUS SEPTUM	SIZE OF OPENING								
Accentuated[8]	5 mo.	Three	One-4 mm. The other two pea-sized	2 mm.	—	1.5-3 mm.	—	—	—	—	PA dilated. Heart 55 grams
Accentuated[28]	18 yr.	Two	5 x 2 mm. 5 x 3 mm.	Closed	—	—	6 mm.	—	—	—	Enlarged right heart
Accentuated split second sound[3]	17 yr.	One	10 x 5 mm.	Closed?	—	—	—	—	—	—	Surgery case. Septum opening with calcium
Split loud[41]	5 yr.	One	5 mm.	Closed	Closed	Large	15 mm.	—	—	—	Heart 260 grams. DM, SM
Snapping P_2 louder than the aortic[40]	2½ yr.	One	3 mm.	Closed	Closed	Dilated	7 mm.	—	7 mm.	—	Heart 130 grams. SM
P_2, snapping, loudest in the pulmonic area[44]	21 yr.	?	?	—	—	—	—	—	—	—	PA dilated. Calcium deposit in septum, 2 cm. SM, DM
Usual single, infantile type[27]	7 wk.	One	2 mm.	ASD 6 x 3.5 mm.	—	Large	Large	Not dilated	Small	—	Persistent left superior vena cava
Accentuated, probably reduplicated, but no true "mitral opening snap"[34]	29 yr.	One*	5-7 mm.	Closed	—	—	10-10.5 mm. dilated	—	Normal	—	PA dilated. PV dilated.* Scattered calcifications around margin

PA—Pulmonary artery. PV—Pulmonary vein. SM—Systolic murmur. DM—Diastolic murmur.
*With a snapping first sound over the mitral area.

A triatrial heart in a 29-year-old man was also corrected by means of hypothermia, inflow occlusion, and open cardiotomy (Lewis and associates,[25] 1956). At operation, the surgeon found that there were no pulmonary veins entering the left atrium, although there appeared to be a single narrow opening into the atrium, high and to the right. Moreover, by needle exploration a high pressure (35 cm. of water) was obtained from the tense posterior chamber, which neither finger could enter by bidigital examination. The anomalous atrial chamber was opened while a finger in the left proper atrium invaginated the abnormal septum into the upper (third) chamber. The septum was then divided under direct vision.

Barrett and Hickie[3] successfully operated on a 17-year-old boy with cor triatriatum. This was accomplished, however, only after the second exploration of the heart. The diagnosis was not made at the time of the first operation, when a normal mitral valve was found.

In June, 1955, when Lam was making a digital exploration of an interatrial septal defect, he could feel the four pulmonary veins but not the mitral valve at

TABLE VI. ELECTROCARDIOGRAPHIC FINDINGS

AUTHOR	FINDINGS
McLester,[28] 1940	Marked right ventricular predominance. Inversion of P_4, T_2, and T_3. Slight notching at the summit of R_3. No other abnormality
Parsons,[32] 1950	Confirmatory evidence of right ventricular hypertrophy. P wave might perhaps be enlarged
Barnes,[2] 1952	Sinus rhythm of 150 per minute. The P waves of 0.3 mv. in Lead II were sharply peaked. There was a right axis shift, with QRS complexes splintered and 0.08 second in duration. V lead showed the pattern of right ventricular hypertrophy
Pedersen,[34] 1954	Sinus rhythm with normal P waves. Pronounced right axis deviation in the standard leads with T inversion in Leads II and III, and in the precordial leads, signs of right ventricular hypertrophy
Becu,[4] 1955	Right ventricular hypertrophy. Probable right atrial enlargement
Petit,[35] 1955	Preponderance of the right heart
Vineberg,[44] 1956	Marked hypertrophy of the right ventricle with signs of strain. Hypertrophy of the right auricle. An electrical axis of −85°
Sawyer,[40] 1957	Sinus tachycardia. Right axis deviation. Right ventricular hypertrophy. Abnormal P waves (tall and notched P waves in Lead II)
Barrett,[3] 1957	Right ventricular hypertrophy. Broad notched P waves
Maxwell,[27] 1957	Right ventricular hypertrophy
Seavey,[41] 1958	Right ventricular hypertrophy
Buffalo Children's Hospital, 1958	Case 2: Normal Case 4: Marked right ventricular hypertrophy with strain pattern on precordial lead

the bottom of the auricle. There was a septal defect. Lam[24] realized that if he closed the defect, the blood from the lungs would be trapped. Because catheterization had indicated two different pressures, the anomaly in question could not be a single ventricle. Fortunately, his finger slipped into the upper defect, thus finding the mitral valve on the other side.

In Pedersen and Therkelsen's case[34] the surgeon's exploring finger failed to detect the anomalous intra-atrial septum; only a normal mitral ostium was felt. A few days later, the patient died. The autopsy revealed an anomalous intra-atrial septum with partial calcification around a small opening (5 by 7 mm.).

Maxwell and associates[27] operated on a 7-week-old male infant with partial anomalous pulmonary venous drainage through a persistent left superior vena cava into the right atrium. They made an anastomosis of the anomalous vein with the left auricular appendage. The patient died on the third postoperative day. The clinical impression was that of left ventricular failure. The autopsy disclosed a cor triatriatum with an anomalous intra-atrial septum in the left atrium, and with an interatrial septal defect in the upper anomalous chamber.

TABLE VII. RADIOGRAPHIC FINDINGS OF THE HEART

AUTHOR	FINDINGS
Patten,[33] 1929	Enlargement of the heart; globular
Palmer,[31] 1930	Considerably enlarged heart
McLester,[28] 1940	No enlargement of the heart (teleoroentgenogram). Slight bulging of the cardiac outline in the region of the left auricle
Pfenning,[36] 1941	Enlarged globular heart
Parsons,[32] 1950	Enlargement and fullness of the left upper border
Edwards,[11] 1951	Generalized enlargement developed within the last 1½ months
Barnes,[2] 1952	Generalized enlargement. Left atrium relatively enlarged
Pedersen,[34] 1954	Normal-sized heart. Cardiothoracic rate 13:26.5 (only pulmonary arch markedly prominent)
Lewis,[25] 1956	No enlargement of the heart. Some prominence of the left atrium and the main pulmonary trunks
Petit,[35] 1955	Enlarged triangular heart. Large bilateral pulmonary condensation
Barrett,[3] 1957	Right ventricular enlargement. No valvular calcification. Enlarged pulmonary arteries
Maxwell,[27] 1957	Generalized cardiac enlargement
Seavey,[41] 1958	Enlarged heart. Prominence of the right ventricle and atrium. Large primary and secondary pulmonary artery segments. Moderate pulmonary congestion
Buffalo Children's Hospital, 1958	Case 2: Enlarged heart Case 4: Slight enlargement of the heart

Apparently, the small hypoplastic left ventricle could not accommodate the larger amount of blood entering through the surgical anastomosis.

In some of the reported cases[7,33] a groove was described on the external surface of the left atrium. On the other hand, a tense chamber could be palpated posterior to and slightly higher than the right atrium.[25] A careful external observation of the atrial chamber might give the surgeon the diagnostic clue, particularly when such observation is linked with some of the catheterization data discussed above. At the present time, this anomaly is certainly correctable by surgery. If a lesion of the mitral ostium or stenosis of the common pulmonary vein is suspected on the basis of the presently available laboratory examinations, including cardiac catheterization and angiocardiography, cardiac surgery is to be highly recommended for the purpose of confirming the diagnosis and, at the same time, for the chance of correcting the anomaly.

TABLE VIII. CARDIAC CATHETERIZATION RESULTS (COR TRIATRIATUM)

AUTHOR	PULMONARY CAPILLARY PRESSURE (MM. Hg)	PULMONARY ARTERY	LEFT ATRIUM	LEFT ACCESSORY UPPER CHAMBER
Pedersen,[31] 1954	Mean 38 – 34	109/72	Mean 7 8	—
Vineberg,[41] 1956	Systole/diastole 45 / 30	Trunk 124/56.7	250 (mm. H_2O)	470 (mm.H_2O)
Lewis,[25] 1956	—	PA 36/15 (Mean 22.5)	35 (cm. H_2O)	—
Sawyer,[40] 1957	Mean 30	Mean 98	—	—
Maxwell,[27] 1957	—	118/56 (Mean 83)	6.4 (Mean)	—
Barrett,[3] 1957	—	—	4	22
Buffalo Children's Hospital, 1958. Case No. 4*	35/52	150/56	25 26	—

*Data will be published in detail by Dr. P. Vlad and Dr. E. Lambert.

SUMMARY

Four cases of the rare congenital anomaly "cor triatriatum" are presented. All pertinent data from the literature, clinical and anatomic, were reviewed, in order to gain more precise information about this congenital heart disease. These data include the electrocardiographic and radiographic findings, and the results of cardiac catheterization and the few surgical operations thus far obtained. The histologic study of the anomalous intra-atrial septum in 2 cases discloses true cardiac muscle fibers contiguous with those of the posterior wall of both chambers in the left atrium.

ADDENDUM

While this report was being prepared for publication, an additional case of cor triatriatum was examined, post mortem, in the Department of Pathology of the Buffalo General Hospital.

Case Report (*Case 5*).—A newborn male infant, cyanotic since birth, died after 36 hours. The following malformations were found: abnormal lobe formations with hypoplastic single lobes representing each lung; absence of the left eyeball; atresia of the esophagus with tracheoesophageal fistula; malrotation of the intestinal tract with elongated membranous transverse mesocolon and an umbilical hernia containing an accessory liver lobe. In addition, the heart presented a cor triatriatum, combined with a high interventricular septal defect and with complete absence of the interatrial septum. It was markedly enlarged, of a somewhat rectangular shape, measuring 2.7 cm. vertically and 4 cm. horizontally. The auricular appendages, especially the left, were dilated. The bilateral pulmonary veins, one from each lung, were united into a single common vein. This common pulmonary vein entered the medial upper posterior portion of the distended left atrium, very close to the upper margin of the inferior vena cava. When the left atrium was viewed posteriorly, there was a shallow longitudinal groove starting upward from the level of the atrioventricular junction. The upper part of the left atrium showed a moderate distention posteriorly. On section, the right atrium disclosed a complete defect of the interatrial septum.

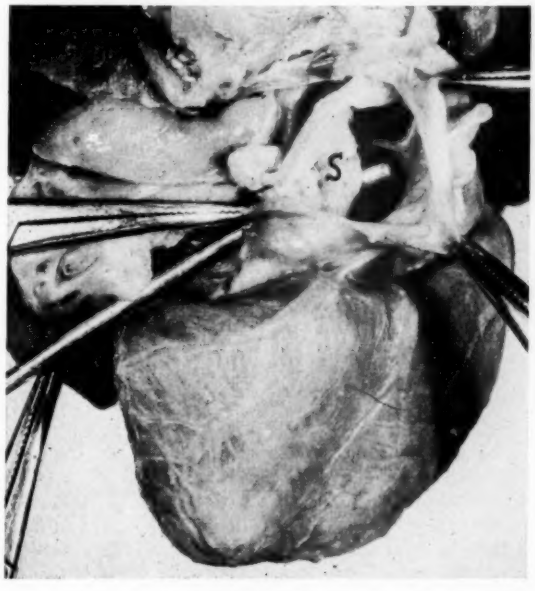

Fig. 7.—Case 5 (Buffalo General Hospital). The posterior wall of the upper chamber of the left atrium is viewed. A probe is inserted from the lower chamber to the upper chamber of the left atrium. A thin bridge-like cord of the right atrium is seen. *S:* Anomalous intra-atrial septum.

The upper border of this defect was at the junction of the right atrium with the superior vena cava, the lower margin above the line of closure of the tricuspid valve. The septal defect measured 15 mm. in length and 6 to 8 mm. in width. There was a bridge-like cord between the anterior wall of the right atrium and the Eustachian valve, which was very thin and about 1 to 2 mm. wide, whereas the cord measured less than 1 mm. in diameter and 8 mm. in length. The cord lay horizontally across the right atrium in a bridge-like fashion. There was a small grayish, almost transparent membranous structure attached anteriorly to the lower border of the interatrial septal defect, 2 to 3 mm. in length and width and less than 1 mm. in thickness: apparently the remnant of the septum primum. When the left atrium was viewed through the interatrial septal defect, an anomalous intra-atrial septum was seen, extending from the posterior wall of the upper medial portion of the left atrium. This septum stretched in a vertical and slightly oblique plane

from anterior superior in posterior inferior direction and separated the left atrium into two chambers, an upper medial posterior and a lower anterior one. At the medial end point the anomalous septum had no direct connection with either anterior or posterior wall of the right atrium. It was 15 mm. long, 6 mm. wide, and 1 mm. thick. The lower anterior chamber of the left atrium contained a distended auricular appendage. The interventricular septal defect, just beneath the medial aortic cusp, measured 5 by 4 mm. The aortic and pulmonic valves measured 18 mm. in circumference. The single pulmonary common vein entered the right upper posterior part of the anomalous upper medial chamber of the left atrium, and its opening was very close to, and slightly above and to the left of, the entrance of the inferior vena cava. Functionally, the predominant direction of flow of the oxygenated blood was much more toward the right atrium because of the presence of the vertical anomalous intra-atrial septum. The right ventricle measured 5 to 7 mm., and the left measured 2 to 3 mm. in thickness. The ductus arteriosus was patent, 9 mm. in circumference. The coronary sinus was small.

Microscopic Findings.—The anomalous intra-atrial diaphragm showed microscopically a thick layer of the cardiac muscle bundles directly connecting with those of the atrial wall. A

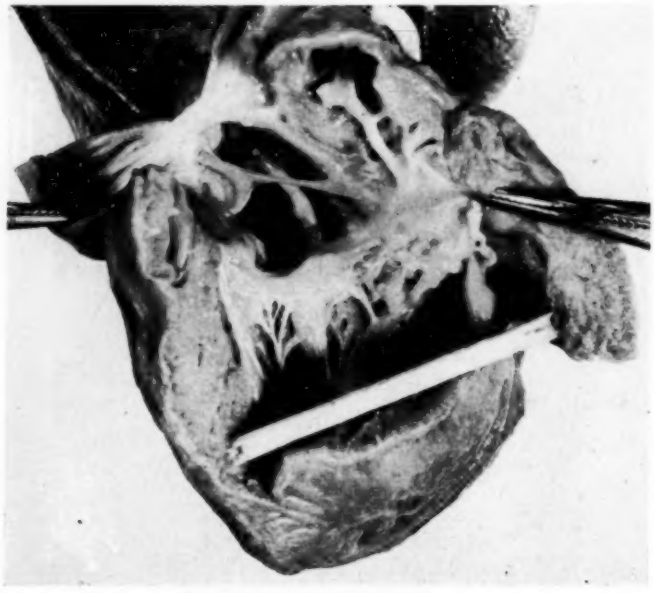

Fig. 8.—Case 5. The right atrium and ventricle are viewed. The vertical but slightly oblique anomalous intra-atrial septum of the left atrium is seen, as is the bridge-like cord of the right atrium. The tricuspid valves are normal.

distinct thickening of the media with marked narrowing of the lumen was seen in only one small arterial branch of the lung. All other arteries and arterioles in the lung sections showed the physiologic hypertrophy of the wall observed in the arteries of the lung at the time of birth.

Comment.—The position and direction of the anomalous intra-atrial septum in the left atrium of this additional case disproves the theory that the septum is an overgrowth of the valve of the foramen ovale. It was shown that the intra-atrial septum originates from the posterior lower part of the upper medial chamber's wall (in the left atrium), and that its medial edge has no direct connection with the anterior wall of both atria nor with the posterior part of the right atrium. These facts indicate clearly that the anomalous intra-atrial septum is not directly related to the formation of the foramen ovale, but rather, to the development of the upper part of the left atrial wall, and that it does not stem from an overgrowth of the right atrial wall.

As previously mentioned, Edwards and associates[11] stated that the accessory chamber of the left atrium results from failure of the common pulmonary vein to become incorporated into

the dorsal wall of the left atrium. The anatomic findings of this additional case support this theory well and, furthermore, explain clearly the initial direction of growth of the anomalous intraatrial septum. This septum originates from the posterior wall of the primitive left atrium and grows in anterior medial direction, apparently during the same period in which the interatrial septum is formed. Therefore, the medial edge of this anomalous intra-atrial septum connects with the (forming) interatrial septal wall, while in process of formation, resulting in several varieties of atrial anomalies. Accordingly, the level of the junction of the anomalous intra-atrial septum with the interatrial septal wall may vary. In Case 5 the anomalous intra-atrial septum (growth) did not meet the interatrial wall because of the latter's complete absence, forming a free medial edge within the left atrium. The association with the complete absence of the interatrial septum, with a bridge-like cord formation of the inferior vena caval valve, and with a high interventricular septal defect, suggest that all these malformations are likely to have originated at the same stage of early embryonal life.

From the hemodynamic point of view, Case 5 of cor triatriatum represents clinically a picture of cor monoatriatum triloculare with interventricular septal defect.

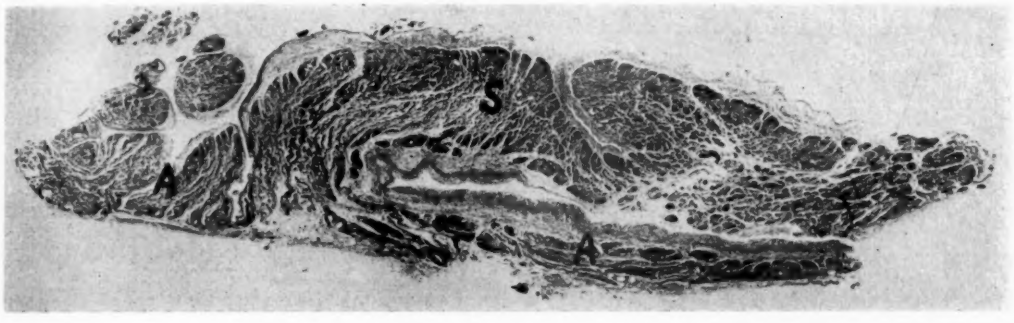

Fig. 9.—Case 5. The anomalous intra-atrial septum (*S*) in horizontal section shows a thick layer of the typical cardiac muscles, which are directly contiguous with those of the posterior wall of both upper and lower chambers of the left atrium (*A*). The endocardium is not thickened.

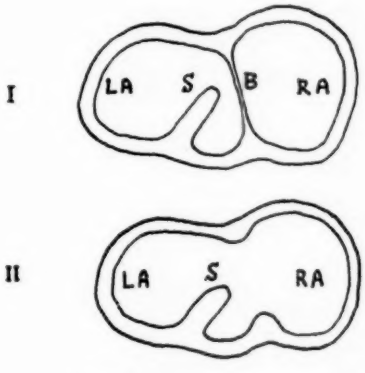

Fig. 10.—Case 5. Two diagrams of different cross sections of the atria illustrate the relationship of the intra-atrial septum in the left atrium. *LA:* Left atrium. *RA:* Right atrium. *S:* Intra-atrial septum. *B:* Bridge-like cord of the right atrium. *I*, Cross section at the mid-level. *II*, Cross section above the level of cross section *I*.

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Annotations

Chlorothiazide in Hypertension

The effect of chlorothiazide on the response of the blood pressure to a single intravenous dose of pentolinium has been studied by Dollery and his associates.[1] A single intravenous dose of chlorothiazide given to 4 hypertensive patients did not affect the response to a dose of pentolinium which followed it. When chlorothiazide was given by mouth for 2 days, however, the blood pressure fell significantly more after the standard intravenous dose of pentolinium, given on the third day, in 9 of 13 hypertensive patients. Eight of these showed at the same time a significant reduction in plasma volume. Of the 5 patients who had no reduction in plasma volume, only one became more sensitive to pentolinium, and this patient showed the greatest degree of sodium depletion in the whole study. The authors conclude that reduction in plasma volume is one of the main factors responsible for the potentiating action of chlorothiazide on ganglion-blocking drugs.

Hollander and Chobanian[2] found no significant change in extracellular volume or sodium space in 12 hypertensive patients given prolonged oral treatment with chlorothiazide, although loss of weight and a reduction in potassium space occurred. These results suggest that the reduction in blood volume is part of a complex rearrangement of water and electrolytes. That reduction in plasma volume by chlorothiazide may not be strictly dependent upon diuresis is suggested by the findings of Rochelle and his co-workers[3] that potentiation of hypotensive drugs by chlorothiazide may be accompanied by a gain, rather than a loss, of body weight. All 13 of Dollery's patients lost weight during treatment with chlorothiazide, and the loss of weight was stated to parallel the degree of diuresis. It would have been interesting to know whether loss of weight and diuresis were related to the reduction in plasma volume, to sodium depletion, or to the degree of potentiation of the action of pentolinium.

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Sinus of Valsalva–Right Heart Communications Due to Congenital Aortic Sinus Defects

Communications between aortic sinuses and right cardiac chambers fall into two basic categories: first, those resulting from rupture of a sinus of Valsalva aneurysm, the structural defect of which may be congenital,[1] syphilitic,[2] or mycotic[3]; and second, those that are present at birth[4]—true congenital connections—occurring in sinuses that are otherwise structurally normal.

In 1839, Hope[5] described "a case of aneurysmal pouch of the aorta bursting into the right ventricle," the first published account of a ruptured congenital aortic sinus aneurysm. Embryologically, this anomaly has been ascribed to defective development of the distal bulbar septum, the structure separating systemic and pulmonary halves of the bulbus cordis.[1] Since only two sinuses can be related to the distal bulbar septum, this thesis is consistent with observations that these aneurysms arise almost exclusively from either a right coronary or noncoronary sinus. However, since cases of what appear to be congenital aneurysms of the left coronary sinus,[6] and indeed of all three sinuses,[7] have been reported, other observers[8] have postulated that the abnormality need not be one of fusion of the bulbar swelling, but rather a developmental error occurring later and involving differentiation of various tissues at the base of the aorta. More recently, histologic study of a congenital aneurysm of the sinus of Valsalva has been published[9] describing the essential lesion as a defect in continuity of the media of the aortic root. Grossly, the developmental aneurysm is either a finger-like projection (diverticulum),[4,9] or a diffuse dilatation of the entire sinus (aneurysm).[10] It is not yet clear whether these two types reflect the same or different embryologic defects. Occasionally, a single aneurysm may give rise to several daughter sinuses.[10] Rupture of these aneurysms occurs with striking preponderance in males, with an age range of 20 to 67 years,[10] although rare instances of perforation at the ages of 4 years,[11] 6 years,[12] 14 years,[13] and 17 years[7] have been reported. In addition to spontaneous perforation, a congenital aneurysm may serve as a nidus for bacterial endocarditis, which in turn may cause rupture,[1] or endocarditis may complicate the course after rupture of a noninfected aneurysm.[9] The sinus usually penetrates into the right atrium or right ventricle,[1,11] occasionally into the pulmonary artery,[14] and rarely into the left ventricle,[15] left atrium,[16] or free pericardial cavity.[17] The event of rupture is ordinarily—but not invariably—heralded by the sudden onset of chest pain suggesting myocardial infarction.[11] That the genesis of the pain is unlikely to be related to encroachment on a coronary ostium is suggested by the frequency with which pain occurs when an aneurysm arises from the noncoronary sinus.[11] Symptoms of congestive cardiac failure may be concomitant or may appear after latent periods of varying durations. Deterioration is typically progressive, although 15-year[17] and 17-year[1] survivals have been reported. The constant difference in pressures between the systemic and venous sides of the perforation generates a continuous machinery-like murmur, and the aortic diastolic reflux may produce a water-hammer pulse.[10,16] Although the presence of the aneurysm generally does not become clinically evident until rupture, cases have been diagnosed occasionally by angiography prior to perforation.[18] Indeed, as blood leaves the unruptured aneurysmal pouch in systole and enters it in diastole, murmurs in both phases of the cardiac cycle may be produced across the mouth of an *intact* aneurysm.[19] Although congenital sinus of Valsalva aneurysms are usually uncomplicated by other lesions, ventricular septal defect is the most frequently associated anomaly.[1,7,20,21] Other cases have been reported with coarctation of the aorta,[22,23] stenosis of the pulmonary conus,[1] and complete heart block[21,25] (which was felt to be causally related in both cases even though one patient also had calcific aortic stenosis). Sinus aneurysms occurring with aortic coarctation deserve comment from the etiological point of view because of the reported association of this lesion with the Marfan syndrome.[26]

The second type of congenital anomaly which results in a communication between sinus of Valsalva and right heart is a malformation *sui generis*.[4] The connection is present at birth and the sinuses are otherwise structurally normal. Congenital connections in this category are exceedingly uncommon. Only five examples could be found in the literature. The first, reported in 1881,[27] was the case of a 30-year-old man who died in marked congestive cardiac failure. Autopsy disclosed two aortic sinuses (bicuspid aortic valve) from one of which originated a smooth membranous, funnel-shaped communication which entered the right heart just distal to a normal pulmonary valve. A membranous ventricular septal defect was also present. Two years later a brief report was published of a 4-month-old male infant[23] who died of enterocolitis, and was found to have a communication between an aortic sinus and right heart. The case reported in 1933,[29] was that of a 1½-year-old male with a bicuspid aortic valve and streptococcal endocarditis engrafted upon a fistulous channel running obliquely from an aortic sinus into the conus of the right ventricle just proximal to the pulmonary valve. In 1949,[30] a detailed account appeared of an autopsy on a 13-year-old male with an endothelized tract extending from the right ventricular infundibulum to the left coronary sinus of Valsalva. This aortic valve had three cusps. Embryologically, the ab-

normal communication was interpreted as an accessory coronary artery, i.e., retention and relative enlargement of an old embryonic channel. The malformations in these four patients consisted of an anatomically similar type of fistulous tract or channel between aortic sinus and right heart. In three the aortic valves were bicuspid. One additional case of this type should be mentioned,[31] since the congenital fistula connected an aortic sinus not with the right heart, but instead with the left ventricle through an 8-mm. tract beneath the anterior leaflet of a tricuspid aortic valve. The only instance of a nonfistulous type of communication was that reported in 1883,[32] of a 53-year-old man who died a noncardiac death and was found to have an orifice connecting a sinus of Valsalva with the right ventricle. The margins were rounded and firm, and "so it appeared quite evident that the opening must have been patent at all times."

With the advent of corrective surgical techniques[33-35] the recognition of communications between aortic sinus and right heart has assumed new significance. The true congenital connections are remarkably rare, but rupture of a congenital sinus of Valsalva aneurysm, although uncommon, is now a well-established clinical entity that is amenable to a rational therapeutic approach.

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The Electrocardiogram in Chagasic Myocarditis

The electrocardiographic abnormalities of chagasic myocarditis have been classified into three main types: (1) intracardiac conduction defects, (2) myocardial damage, and (3) cardiac arrhythmias.

1. *Intracardiac Conduction Defects.*—(a) Right bundle branch block, either complete or incomplete, is the most common intraventricular defect. Rosenbaum and associates[3] and Pinto Lima and associates[4] report its incidence as varying from 51.31 to 55.7 per cent, the complete type of block being more frequent (48.68 per cent) and having a characteristic behavior. (b) Left bundle branch block is a less common type of intraventricular conduction defect. Its incidence varies from 2.6 per cent in clinical cases to 38.15 per cent in autopsy cases, the complete type being observed more frequently. In 45 per cent of the cases with complete LBBB, a Q wave was present in Leads L_1, VL, and V_5 while pathologic examination showed septal fibrosis with normal coronary arteries.[4] (c) Another type of intraventricular conduction defect is represented by wide, positive, slurred QRS complexes in all precordial leads (7.76 per cent). Pinto Lima and associates[4] have interpreted such findings as bilateral bundle branch block or RBBB with an important right ventricular enlargement as being responsible for the registration of characteristic QRS complexes from Lead V_1 to Lead V_6. (Right ventricular enlargement was found at postmorten examination.) (d) A-V conduction defects were either complete (from 4.4 to 18.54 per cent) or incomplete (from 7 to 17.35 per cent).[3,4]

2. *Myocardial Damage.*—(a) Repolarization abnormalities: Abnormal T waves, always of the "primary" type, were a frequent finding (43 per cent). They were present in almost one out of two cases with chagasic RBBB, whereas nonchagasic RBBB always showed "secondary" T-wave changes.[3] (b) Electrical signs of necrosis: Myocardial injury of the apex of the heart, with obvious thinning of the left ventricle, was found by Carvalhao and associates[1] in 20 out of 23 autopsy cases. This might have been due to necrotic damage brought on by the inflammatory process and/or local circulatory obstruction due to focal endarteritis with thickening of the intima. The ECG showed alterations indicative of apical necrosis in 10 of those 23 cases; 5 tracings were considered "typical" and 5 more were considered "suggestive." The so-called "typical" pattern was a low voltage of the R wave in some precordial leads between Lead V_1 and Lead V_5, or, at least, its reduction in one precordial lead in comparison with the previous one. The so-called "suggestive" pattern was a leftward displacement of the transitional zone, with persistently low voltage of the R wave in those leads in which the "left ventricular" elevation of the R wave might have been expected. The authors[1] point out that this pattern does not always correspond with the autopsy finding of right ventricular enlargement. (c) Ventricular mean manifest vectors: In the particular case of chagasic RBBB the spatial orientation of SÂQRS (ventricular activation vector) usually lies between −60 and −90°, having a forward orientation in 46 out of 50 cases. The terminal

vectors of QRS, in contrast to the usual distribution found in RBBB of nonchagasic patients, lay between −100 and −150°. The SÂT vector (mean manifest vector of repolarization) was definitely opposite to the SÂQRS. The superior, leftward, and forward orientation of SÂQRS in RBBB is probably related to the autopsy findings of diffuse myocardial damage with biventricular dilatation and left ventricular hypertrophy plus myocardial fibrosis of the heart apex.[4]

3. *Cardiac Arrhythmias.*—Aristóteles Brasil[2] considers that a sinus bradycardia or abnormally fixed sinus rhythm, associated with chagasic myocarditis and obvious heart failure, is due to partial or complete block of the autonomous nervous system. It may also be due to important damage to the sinus node itself, because the bradycardia is not modified by artificial fever. As far as ectopic rhythms are concerned, all types of extrasystoles were found in 75.8 per cent, and multifocal ventricular extrasystoles in 45.96 per cent, of chagasic patients.[4] The combination of ventricular extrasystoles and RBBB was found in 49.2 per cent of the cases,[3] and these two characteristics plus "primary" T-wave changes were found in 31.7 per cent.[3] Auricular fibrillation was found in 14 out of 130 cases, usually associated with severe heart failure or important cardiac enlargement, giving rise, then, to a grave prognosis.[3]

It may be concluded from the medical literature that the electrocardiogram is a sensitive and specific diagnostic aid in the identification of cardiac involvement in Chagas disease. It is the only means of proving the presence of chagasic myocarditis in an early stage of the disease. Extrasystoles of all types represent the electrocardiographic abnormality with the highest incidence, although they have a low specific value in many other instances. On the other hand, a sinus bradycardia or an abnormally fixed sinus rhythm in the presence of heart failure seem to be highly specific signs, although unfortunately of a low incidence. RBBB with SÂQRS peculiarly oriented to the left and upward is both a frequent and highly specific sign. This type of RBBB, associated with multifocal ventricular extrasystoles or with "primary" T-wave changes, is very characteristic of chagasic myocarditis and practically guarantees its diagnosis in geographic zones in which Chagas disease is endemic.

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The Evolution of Methodology in Hemodynamic Research

A recent book by Dr. Carl J. Wiggers,[1] written in memoir form, evokes anew in the reader a keen appreciation of the tremendous strides which this investigator and his lineal scientific descendants have made in the field of cardiovascular dynamics during the past forty-odd years. Although we do not subscribe completely to the dictum, "Die Methode ist alles" (unless "method" includes the human mind as an analog computer), Wiggers' scientific history does serve to emphasize the fundamental importance of methodology in research. Having introduced the Frank optical capsule into this country, with certain important modifications of his own, Wiggers made available a highly accurate technique for the registration of cardiovascular intraluminal pressures. The dynamic validity of the technique was confirmed by the late Dr. Dayton C. Miller, who was professor of physics at the Case Institute of Technology and an internationally renowned authority on the science of sound.

Valuable modifications of the optical manometer were later made by Hamilton, Gregg, and Green. During the past dozen years or so, however, electromechanical pressure gauges have largely replaced the older but simpler optical device. Electrical transducers do offer certain advantages—particularly ready adjustment of sensitivity, increased control of damping characteristics, and exceptionally great sensitivity without loss of adequate frequency response.

Since 1940, the scope of hemodynamic studies has expanded widely, but generally with a considerable loss of technical quality. Both of these developments, the desirable and undesirable alike, are the inevitable consequence of cardiac catheterization. The open-tip catheter is simply not the dynamic peer of the apparatus to which it transmits hemodynamic information. (In this connection we believe than Hansen's monograph[2] should be required reading for anyone who is seriously engaged in hemodynamic research.) Despite the dynamic inadequacies of the cardiac catheter it is capable of yielding information of great importance, provided that artefactual oscillations and deflections are not misinterpreted.

Apparently the most likely solution to the catheter problem lies in migration of the transducer from the distal to the proximal end. For this reason a manometric sound, armed at its distal end with a miniature differential-transformer type of pressure sensing device, was constructed by Wetterer,[3] and later refined by Gauer and associates.[4] More recently, engineers at the Ford Foundation have developed a strain-gauge type of manometric sound. It is a tribute to their ingenuity that the device produces excellent pressure tracings even though it generates impulses of only a few microvolts' magnitude. In standard transducer amplifiers, electrical impulses of this amplitude fall virtually within the allowable "noise" limit.

There have been recent attempts to record the velocity of phasic blood flow at the catheter tip. The validity of the technique depends essentially upon the accurate sensing of small differential pressures. Although the originally published illustrations[5] show obvious artefacts in the raw pressure information, a later report[6] indicates good correlation of phasic flows recorded in this manner as compared with simultaneous registration by two other methods. If the validity of the technique can be further substantiated, it should prove to be an important advance in the methodology of hemodynamic investigation.

Most of the contributions to hemodynamic methodology made in the modern era of electron-tube technology are genuinely valuable, but their relative complexity emphasizes once again the simplicity and elegance of research methods used during the Wiggers era.

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Announcements

POSTDOCTORAL TRAINING IN EITHER CLINICAL OR EXPERIMENTAL CARDIOLOGY is offered by the Division of Cardiology of The Chicago Medical School at Mount Sinai Hospital, Chicago, Ill. The program of training is supported by the National Heart Institute, U.S.P.H.S.

Physicians having some training in Clinical Cardiology or having a Ph.D. in Experimental Physiology will receive preference.

Information concerning the program of training and stipend may be obtained by writing to Dr. A. A. Luisada, Program Director, 2755 West 15th St., Chicago 8, Ill.

THE INSTITUTE FOR ADVANCEMENT OF MEDICAL COMMUNICATION, New York City, has received grant support from the U. S. Public Health Service for three current studies and projects aimed at improving intraprofessional communication in the medical sciences. A program for training investigators to study the general processes by which the results of medical research are disseminated, and by which the informational needs of research workers are met, is being supported by a grant from the National Heart Institute. The Division of General Medical Sciences, National Institutes of Health, has awarded a grant to organize the Council of Medical Television. The fate of information evolving from research in the new field of psychopharmacology is being studied under a grant from the National Institute of Mental Health.

ERRATUM

The paper, "The Simultaneous Estimation of Right and Left Ventricular Outputs Applied to a Study of the Bronchial Circulation in Patients With Chronic Lung Disease," by Cudkowicz, et al., which was published in the AMERICAN HEART JOURNAL 58:743, 1959, was received for publication on March 9, 1959, rather than on July 6, 1959.